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Variants of tumor involved genes

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Signature of Applicant

For the Applicants,
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By : —

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ווריאנטים של גנים המעורבים בסרטן

Variants of tumor involved genes

Compugen Ltd.

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SPLICE VARIANTS OF ONCOGENES

FIELD OF THE INVENTION

The present invention concerns novel nucleic acid sequences, vectors and host cells containing them, amino acid sequences encoded by said sequences, and antibodies reactive with said amino acid sequences, as well as pharmaceutical compositions comprising any of the above. The present invention further concerns methods for screening for candidate activators or deactivators utilizing said amino acid sequences. The invention also concerns diagnostic assays utilizing said sequences.

BACKGROUND OF THE INVENTION

Many genes which are involved with tumors are involved with functions which encourage and promote growth and division of cells. Some tumor-involved cells are expressed only in tumor cells, while others are expressed also in normal cells albeit at lower levels. A specific example of tumor-involved genes are oncogenes, which are muted formed of proto-oncogenes.

Generally, proto-oncogenes code for cellular proteins that relay signals to the cell's nuclei thus stimulating growth. These cellular proteins respond to signals from other cells and the signaling process involves several steps among them binding of growth and proliferation regulating factors to the cell membrane, release of second messenger, and a host of other intermediates, in the cell cytoplasm, and activation in the nucleus of transcription factors which move the cells through their growth cycles.

Proto-oncogenes that code for these various components in the cascade may mutate, thus becoming oncogenes that keep the pathways continuously active regardless of the extracellular signals received by the cell. This may result in over-production of growth factors, flooding of the cell with replication signals, uncontrolled stimulation of the intermediary pathways and unrestrained cell growth driven by elevated levels of transcription factors.

The activation of a proto-oncogene to express its oncogenic potential may occur due to point mutation, chromosome rearrangement, gene amplification (an increase in the number of copies of normal proto-oncogenes within a cell) and viral insertion resulting in the control of the expression of the proto-oncogene by a more active promoter.

Typically, oncogenes exhibit dominant phenotype at the cellular level, i.e. one copy of an activated oncogene is sufficient to produce its oncogenic effect, a phenomena which is termed *"gain of function"*. There is usually a requirement to have more than one mutation in the proto-oncogene in order to change a normal cell line into neoplasia. The oncogene may be transmitted from generation to generation when a proto-oncogene mutates in the germ line, and since as indicated above usually more than one mutation is required, a single mutation results in a dominantly inherited tumor predisposition.

The detection of oncogene is of major importance in the detection of tumors as well as in the detection of predisposition to a specific kind of tumor, which may result from additional mutations on an already mutated pro-oncogene. Oncogenes are detected by a plurality of methods among them PCR amplification, hybridization, as well as detection of the oncogenic product by various immunoassays. The understanding of the site of activity of the oncogene is of course of a major importance in the designing of a suitable therapeutical model for the treatment of the cancer resulting from the activity of said oncogene.

Alternative splicing (AS) is an important regulatory mechanism in higher eukaryotes (P.A. Sharp, *Cell* 77, 805-8152 (1994). It is thought to be one of the most important mechanisms for differential expression related to tissue or development stage specificity. AS influences also: protein stability, protein clearance as well as tissue and cellular localization As may further alter protein function by increasing or decreasing the functionality,and may further affect post translational modifications, It is known to play a major role in numerous biological systems, including human antibody responses, and sex determination in *Drosophila*, (S. Stamm, M.Q. Zhang, T.G. Marr and D.M. Helfman, *Nucleic*

Acids Research **22**, 1515-1526 (1994); B. Chabot, *Trends Genet.* **12**, 472-478 (1996); R.E. Breitbart, A. Andreadis, B. Nadal-Ginard, *Annual Rev. Biochem.*, **56**, 467-495 (1987); C.W. Smith, J.G. Patton, B. Nadal-Ginard, *Annu. Rev. Genet.*, **27**, 527-577 (1989)).

Until recently it was commonly believed that alternative splicing existed in only a small fraction of genes (about 5%). A recent observation based on literature survey of known genes revises this conservative estimate to as high as an estimate that at least 30% of human genes are alternatively spliced (M.S. Gelfand, I. Dubchak, I. Draluk and M. Zorn, *Nucleic Acids Research* **27**, 301-302 (1999). The importance of the actual frequency of this phenomenon lies not only in the direct impact on the number of proteins created (100,000 human genes, for example, would be translated to a much higher number of proteins), but also in the diversity of functionality derived from the process.

Several mechanisms at different stages may be held responsible for the complexity of higher eukaryote which include: alternative splicing at the transcription level, RNA editing at the post-transcriptional level, and post-translational modifications are the ones characterized to date.

GLOSSARY

In the following description and claims use will be made, at times, with a variety of terms, and the meaning of such terms as they should be construed in accordance with the invention is as follows:

"Tumor-involved genes (TIG)" – genes for which there is some scientific indication linking their function, expression, or change in the level of their expressionto tumors. This term does not signify necessarily that the genes cause the tumor (although in some cases this is so) but may also indicate that the genes are a result of the tumor process, for example, they are activated by other genes which are the cause of the tumor.

"Variant nucleic acid sequence" – the sequence shown in any one of SEQ ID NO: 1 to SEQ ID NO: 36, sequences having at least *90% identity* (see below) to said sequence and *fragments* (see below) of the above sequences of least 20 b.p. long. These sequences are sequences coding for a novel, naturally occurring, alternative splice variants of native and known genes which are *tumor-involved genes (TIG)*. It should be emphasized that the novel variants of the present invention are naturally occurring sequences resulting from alternative splicing of the TIGS and not merely truncated, mutated or fragmented forms of known tumor-involved sequences which are artificially produced.

"Variant product – also referred at times as the "variant protein" or ***"variant polypeptide"*** – is an amino acid sequence encoded by the variant nucleic acid sequence which is a naturally occurring mRNA sequence obtained as a result of alternative splicing. The amino acid sequence may be a peptide, a protein, as well as peptides or proteins having *chemically modified* amino acids (see below) such as a glycopeptide or glycoprotein. The variant products are shown in any one of SEQ ID NO: 37 to SEQ ID NO: 72. The term also includes *homologues* (see below) of said sequences in which one or more amino acids has been added, deleted, *substituted* (see below) or *chemically modified* (see below) as well as *fragments* (see below) of this sequence having at least 10 amino acids.

"Nucleic acid sequence" – a sequence composed of DNA nucleotides, RNA nucleotides or a combination of both types and may includes natural nucleotides, chemically modified nucleotides and synthetic nucleotides.

"Amino acid sequence" – a sequence composed of any one of the 20 naturally appearing amino acids, amino acids which have been *chemically modified* (see below), or composed of synthetic amino acids.

"Fragment of variant nucleic acid sequence" – novel short stretch of nucleic acid sequences of at least 20 b.p., which does not appear as a continuous stretch in the *original-nucleic acid sequence* (see below). The fragment may be a sequence which was previously undescribed in the context of the published RNA and which affects the amino acid sequence encoded by the known oncogene. For example, where the variant nucleic includes a sequence which was not included in the original sequence of the oncogene (for example a sequence which was an intron in the original sequence) the fragment may contain said additional sequence. The fragment may also be a region which is not an intron, which was not present in the original sequence of the TIG. For example where the variant lacks a non-terminal region which was present in the original sequence of the TIG. The two stretches of nucleotides spanning this region (upstream and downstream) are brought together by splicing in the variant, but are spaced from each by the spliced out region in the original sequence of the TIG and are thus not continuous in the original sequence. A continuous stretch of nucleic acids comprising said two sparing stretches of nucleotides is not present in the original sequence of the TIG and thus falls under the definition of fragment.

"Fragments of variant products" - novel amino acid sequences coded by the *"fragment of variant nucleic acid sequence"* defined above.

"Homologues of variants" – amino acid sequences of variants in which one or more amino acids has been added, deleted or replaced. The addition, deletion or replacement should be in the regions or adjacent to regions where the variant differs from the *original sequence* (see below) of the TIG.

"Conservative substitution" - refers to the substitution of an amino acid in one class by an amino acid of the same class, where a class is defined by common physicochemical amino acid side chain properties and high substitution frequencies in homologous proteins found in nature, as determined, for example,

by a standard Dayhoff frequency exchange matrix or BLOSUM matrix. [Six general classes of amino acid side chains have been categorized and include: Class I (Cys); Class II (Ser, Thr, Pro, Ala, Gly); Class III (Asn, Asp, Gln, Glu); Class IV (His, Arg, Lys); Class V (Ile, Leu, Val, Met); and Class VI (Phe, Tyr, Trp). For example, substitution of an Asp for another class III residue such as Asn, Gln, or Glu, is a conservative substitution.

"Non-conservative substitution" - refers to the substitution of an amino acid in one class with an amino acid from another class; for example, substitution of an Ala, a class II residue, with a class III residue such as Asp, Asn, Glu, or Gln.

"Chemically modified" - when referring to the product of the invention, means a product (protein) where at least one of its amino acid resides is modified either by natural processes, such as processing or other post-translational modifications, or by chemical modification techniques which are well known in the art. Among the numerous known modifications typical, but not exclusive examples include: acetylation, acylation, amidation, ADP-ribosylation, glycosylation, GPI anchor formation, covalent attachment of a lipid or lipid derivative, methylation, myristlyation, pegylation, prenylation, phosphorylation, ubiqutination, or any similar process.

"Biologically active" - refers to the variant product having some sort of biological activity, for example, some physiologically measurable effect on target cells, molecules or tissues.

"Immunologically active" defines the capability of a natural, recombinant or synthetic varient product, or any fragment thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies. Thus, for example, an immunologically active fragment of variant product denotes a fragment which retains some or all of the immunological properties of

the variant product, e.g can bind specific anti-variant product antibodies or which can elicit an immune response which will generate such antibodies or cause proliferation of specific immune cells which produce variant.

"Optimal alignment" - is defined as an alignment giving the highest percent identity score. Such alignment can be performed using a variety of commercially available sequence analysis programs, such as the local alignment program LALIGN using a ktup of 1, default parameters and the default PAM. A preferred alignment is the one performed using the CLUSTAL-W program from MacVector (TM), operated with an open gap penalty of 10.0, an extended gap penalty of 0.1, and a BLOSUM similarity matrix. If a gap needs to be inserted into a first sequence to optimally align it with a second sequence, the percent identity is calculated using only the residues that are paired with a corresponding amino acid residue (i.e., the calculation does not consider residues in the second sequences that are in the *"gap"* of the first sequence). In case of alignments of known gene sequences with that of the new variant, the optimal alignment invariably included aligning the identical parts of both sequences together, then keeping apart and unaligned the sections of the sequences that differ one from the other.

"Having at least 90% identity" - with respect to two amino acid or nucleic acid sequences, refers to the percentage of residues that are identical in the two sequences when the sequences are optimally aligned. Thus, 90% amino acid sequence identity means that 90% of the amino acids in two or more optimally aligned polypeptide sequences are identical, however this definition explicitly excludes sequences which are 100% identical with the original sequence from which the variant of the invention was varied.

"Isolated nucleic acid molecule having an variant nucleic acid sequence" - is a nucleic acid molecule that includes the coding variant nucleic acid sequence. Said

isolated nucleic acid molecule may include the variant nucleic acid sequence as an independent insert; may include the variant nucleic acid sequence fused to an additional coding sequences, encoding together a fusion protein in which the variant coding sequence is the dominant coding sequence (for example, the additional coding sequence may code for a signal peptide); the variant nucleic acid sequence may be in combination with non-coding sequences, e.g., introns or control elements, such as promoter and terminator elements or 5' and/or 3' untranslated regions, effective for expression of the coding sequence in a suitable host; or may be a vector in which the variant protein coding sequence is a heterologous.

"Expression vector" - refers to vectors that have the ability to incorporate and express heterologous DNA fragments in a foreign cell. Many prokaryotic and eukaryotic expression vectors are known and/or commercially available. Selection of appropriate expression vectors is within the knowledge of those having skill in the art.

"Deletion" - is a change in either nucleotide or amino acid sequence in which one or more nucleotides or amino acid residues, respectively, are absent.

"Insertion" or "addition" - is that change in a nucleotide or amino acid sequence which has resulted in the addition of one or more nucleotides or amino acid residues, respectively, as compared to the naturally occurring sequence.

"Substitution" - replacement of one or more nucleotides or amino acids by different nucleotides or amino acids, respectively. As regards amino acid sequences the substitution may be conservative or non- conservative.

"Antibody" – refers to IgG, IgM, IgD, IgA, or IgG antibody. The definition includes polyclonal antibodies or monoclonal antibodies. This term refers to

whole antibodies or fragments of the antibodies comprising the antigen-binding domain of the anti-variant product antibodies, e.g. antibodies without the Fc portion, single chain antibodies, fragments consisting of essentially only the variable, antigen-binding domain of the antibody, etc.

Distinguishing antibody" – an antibody capable of binding to the variant product and not the original amino acid sequence of the tumor-involved gene from which it has been varied, or an antibody capable of binding to the original nucleic acid sequence and not to the variant product.

"Activator" - as used herein, refers to a molecule which mimics the effect of the natural variant product or at times even increases or prolongs the duration of the biological activity of said product, as compared to that induced by the variant product. The mechanism may be by any mechanism known to prolonging activities of biological molecules such as binding to receptors; prolonging the lifetime of the molecules; increasing the activity of the molecules on its target; increasing the affinity of molecules to its receptor; inhibiting degradation or proteolysis of the molecules, or mimicking the biological activity of the variants on their targets, etc. Activators may be polypeptides, nucleic acids, carbohydrates, lipids, or derivatives thereof, or any other molecules which can bind to and activate the variant product.

"Deactivator" or ***("Inhibitor")*** - refers to a molecule which modulates the activity of the variant product in an opposite manner to that of the activator, by decreasing or shortening the duration of the biological activity of the variant product. This may be done by any mechanism known to deactivate or inhibit biological molecules such as block of the receptor, block of active site, competition on binding site in target, enhancement of degradation, etc. Deactivators may be polypeptides, nucleic acids, carbohydrates, lipids, or

derivatives thereof, or any other molecules which bind to and modulate the activity of said product.

"Treating a disease" - refers to administering a therapeutic substance effective to ameliorate symptoms associated with a disease, to lessen the severity or cure the disease, or to prevent the disease from occurring. Typically the disease is cancer.

"***Detection***" – refers to a method of detection of a cancer. This term may refer to detection of a predisposition to cancer as well as for establishing the prognosis of the patient by determining the severity of the disease, i.e. determining in which stage the cancer is.

"Probe" – the variant nucleic acid sequence, or a sequence complementary therewith, when used to detect presence of other similar sequences in a sample. The detection is carried out by identification of hybridization complexes between the probe and the assayed sequence. The probe may be attached to a solid support or to a detectable label.

"Original sequence" – the amino acid or nucleic acid sequence of the tumor-involved gene (TIG) from which the variant of the invention have been varied as a result of alternative slicing. This sequence will also be referred to at times as *"tumor-involved-gene" (TIG)*.

SUMMARY OF THE INVENTION

The present invention is based on the finding of several novel, naturally occurring splice variants, which are naturally occurring sequences obtained by alternative splicing of known genes which expression was reported in scientific literature to be involved with tumors (hereinafter *"tumor-involved genes"* or *"TIGS"*). The above term does not signify that the gene necessarily caused the

tumor (although this may be so), merely that they are involved therewith (i.e. expressed in tumors) and this expression may be the result of other effects, for example, as a result of expression of other genes. The novel splice variants of the invention are not merely truncated forms, fragments or mutations of the known tumor-involved genes, but rather novel sequences which naturally occur within the body of individuals, and thus have physiological significance.

The term *"alternative splicing"* in the context of the present invention and claims refers to: intron inclusion, exon exclusion, addition or deletion of terminal sequences in the variant as compared to the original sequences, as well as to the possibility of *"intron retention"*. Intron retention is an intermediate stage in the processing of RNA transcripts, where prior to production of fully processed mRNA the intron (naturally spliced in the original TIG sequence) is retained in the variant. These intermediately processed RNAs may have physiological significance and are also within the scope of the invention.

The novel variant products of the invention may have the same physiological activity as the original tumor-involved peptide from which they have been varied (although perhaps at a different level); may have an opposite physiological activity from the activity featured by the original tumor-involved peptide from which they are varied; may have a completely different, unrelated activity to the activity of the original tumor-involved peptide which they are varied; or alternatively may have no activity at all and this may lead to various diseases or pathological conditions, especially cancer. Both in the case the variant has the same activity as well as the case it has the opposite activity as the original TIG sequence, it may differ from the TIG in its stability, its clearance rate and rate of degradation its tissue and cellular localization, its ligand specificity, its cellular distribution, its temporal expression pathway, manner for up and down regulation and in other biological properties not necessarily connected to activity.

The novel variants may also serve for detection purposes, i.e. their presence or level may be cancer, a predisposition to cancer or the stage and aggression of the cancer disease, or alternatively the ratio between the level variants and the level

original peptide from which they were varied, or the ratio to other variants (all obtained by alternative splicing from the same original sequence of the tumor-involved gene) may be indicative of the presence of cancer, predisposition to cancer or the stage and aggressiveness of the cancer disease.

For example, for detectional purposes, it is possible to establish differential expression of various variants in various tissues. A certain variant may be expressed mainly in one tissue, while the original sequence (tumor-involved sequence) from which it has been varied, or another variant (obtained by alternative splicing from the same original tumor-involved sequence) may, be expressed mainly in another tissue. Understanding of the distribution of the variants in various tissues may be helpful in basic research, for understanding the physiological function of the original tumor-involved genes from which they have been varied, as well as help in targeting pharmaceuticals or in developing pharmaceuticals, and in establishing more accurate modalities of diagnosis.

The study of the variants may also be helpful in distinguishing various stages in the life cycles of the same type of cells which may also be helpful for development of pharmaceuticals for various cancer stages in which cell cycles is non-normal.

Thus the detection may by determination of the presence or the level of expression of the variant within a specific cell population, comparing said presence or level between various cell types in a tissue, between different tissues and between individuals.

Thus the present invention provides by its first aspect, a novel isolated nucleic acid molecule comprising or consisting of any one of the coding sequence SEQ ID NO: 1 to SEQ ID NO: 36, fragments of said coding sequence having at least 20 nucleic acids (provided that said fragments are continuous stretches of nucleotides not present in the original sequence from which the variant was varied), or a molecule comprising a sequence having at least 90%, identity to SEQ ID NO: 1 to SEQ ID NO: 36, provided that the molecule is not completely identical to

the original sequence of the tumor-involved gene from which the variant was varied.

The present invention further provides a protein or polypeptide comprising or consisting of an amino acid sequence encoded by any of the above nucleic acid sequences, termed herein *"variant product"*, for example, an amino acid sequence having the sequence as depicted in any one of SEQ ID NO: 37 to SEQ ID NO: 72, fragments of the above amino acid sequence having a length of at least 10 amino acids coded by the above fragments of the nucleic acid sequences, as well as homologues of the above amino acid sequences in which one or more of the amino acid residues has been substituted (by conservative or non-conservative substitution) added, deleted, or chemically modified.

The deletions, insertions and modifications should be in regions, or adjacent to regions, wherein the variant differs from the original sequence of the tumor-involved gene.

For example, where the variant is different from the original sequence of the tumor-involved gene by addition of a short stretch of 10 amino acids, in the terminal or non- terminal portion of the peptide i.e. inclusion of an exon, the invention also concerns homologues of that variant where the additional short stretch is altered for example, it includes only 8 additional amino acids, includes 13 additional amino acids, or it includes 10 additional amino acids, however some of them being conservative or non-conservative substitutes of the original additional 10 amino acids of the novel variants. In all cases the changes in the homolog, as compared to the original tumor-involved sequence, are in the same regions where the variant differs from the original sequence, or in regions adjacent to said region.

Another example is where the variant lacks a non-terminal region (for example of 20 amino acids) which is present in the original tumor-involved sequence (due for example to exon exclusion). The homologues may lack in the same region only 17 amino acids or 23 amino acids. Again the deletion is in the same region where the variant lacks a sequence as compared to the original tumor-involved sequence, or in a region adjacent thereto. It should be appreciated

that once a man versed in the art's attention is directed to the importance of a specific region, due to the fact that this region differs in the variant as compared to the original sequence of the tumor-involved gene, there is no problem in derivating said specific region by addition to it, deleting from it, or substituting some amino acids in it. Thus homologues of variants which are derivated from the variant by changes (deletion, addition, substitution) only in said region as well as in regions adjacent to it are also a part of the present invention. Generally, if the variant is distinguished from the original sequence of the tumor-involved gene by some sort of physiological activity, then the homolog is distinguished from the original tumor-involved sequence in essentially the same manner.

The present invention further provides nucleic acid molecule comprising or consisting of a sequence which encodes the above amino acid sequences, (including the fragments and homologues of the amino acid sequences). Due to the degenerative nature of the genetic code, a plurality of alternative nucleic acid sequences, beyond those depicted in any one of SEQ ID NO: 1 to SEQ ID NO: 36, can code for the amino acid sequences of the invention. Those alternative nucleic acid sequences which code for the same amino acid sequences as coded by the sequence SEQ ID NO: 1 to SEQ ID NO: 36 (i.e. SEQ ID NO: 37 to SEQ ID NO: 72) are also an aspect of the of the present invention.

The present invention further provides expression vectors and cloning vectors comprising any of the above nucleic acid sequences, as well as host cells transfected by said vectors.

The present invention still further provides pharmaceutical compositions comprising, as an active ingredient, said nucleic acid molecules, said expression vectors, or said protein or polypeptide.

These pharmaceutical compositions are suitable for the treatment of various cancers, which can be ameliorated or cured by raising the level of any one of the variant products of the invention.

By a second aspect, the present invention provides a nucleic acid molecule comprising or consisting of a non-coding sequence which is complementary to that

of any one of SEQ ID NO: 1 to SEQ ID NO: 36, or complementary to a sequence having at least 90% identity to said sequence (with the proviso added above) or a fragment of said two sequences (according to the above definition of fragment). The complementary sequence may be a DNA sequence which hybridizes with any one of SEQ of ID NO: 1 to SEQ ID NO: 36 or hybridizes to a portion of that sequence having a length sufficient to inhibit the transcription of the complementary sequence. The complementary sequence may be a DNA sequence which can be transcribed into an mRNA being an antisense to the mRNA transcribed from any one of SEQ ID NO: 1 to SEQ ID NO: 36 or into an mRNA which is an antisense to a fragment of the mRNA transcribed from any one of SEQ ID NO: 1 to SEQ ID NO: 36 which has a length sufficient to hybridize with the mRNA transcribed from SEQ ID NO: 1 to SEQ ID NO: 36, so as to inhibit its translation. The complementary sequence may also be the mRNA or the fragment of the mRNA itself.

The nucleic acids of the second aspect of the invention may be used for therapeutic or diagnostic applications for example as probes used for the detection of the variants of the invention. The presence of the variant transcript or the level of the variant transcript may be indicative of cancer, predisposition to cancer or the stage or aggressiveness of the cancer disease. In addition or alternatively, the ratio of the level of the transcripts of the variants of the invention may also be compared to that of the transcripts of the original sequences of the oncogenes from which have been varied, or to the level of transcript of other variants (especially obtained by alternative splicing from the same original sequence), and said ratio may be indicative of cancer, predisposition to cancer or the stage or aggressiveness of the cancer disease

The present invention also provides expression vectors comprising any one of the above defined complementary nucleic acid sequences and host cells transfected with said nucleic acid sequences or vectors, being complementary to those specified in the first aspect of the invention.

The invention also provides anti-variant product antibodies, namely antibodies directed against the variant product which specifically bind to said variant product. Said antibodies are useful both for diagnostic and therapeutic purposes. For example said antibody may be as an active ingredient in a pharmaceutical composition as will be explained below.

The present invention also provides pharmaceutical compositions comprising, as an active ingredient, the nucleic acid molecules which comprise or consist of said complementary sequences, or of a vector comprising said complementary sequences. The pharmaceutical composition thus provides pharmaceutical compositions comprising, as an active ingredient, said anti-variant product antibodies.

The pharmaceutical compositions comprising said anti-variant product antibodies or the nucleic acid molecule comprising said complementary sequence, are suitable for the treatment of diseases and pathological conditions where a therapeutically beneficial effect may be achieved by neutralizing the variant (either at the transcript or product level) or decreasing the amount of the variant product or blocking its binding to its target, for example, by the neutralizing effect of the antibodies, or by the effect of the antisense mRNA in decreasing the expression level of the variant sequence. In particular these diseases are cancer diseases and the treatment may also be for amelioration of cancer or for prevention of cancer purposes.

According to the third aspect of the invention the present invention provides methods for detecting the level of the transcript (mRNA) of said variant product in a body fluid sample, or in a specific tissue sample, for example by use of probes comprising or consisting of said coding sequences; as well as methods for detecting levels of expression of said product in tissue, e.g. by the use of antibodies capable of specifically reacting with the variant products of the invention. Detection of the level of the expression of the variant of the invention in particular as compared to that of the original tumor-involved gene sequence from which it was varied or compared to other variant sequences all varied from the same original TIG

sequence may be indicative of a cancer, predisposition to cancer or the stage or aggressiveness of the cancer disease

The method, according to this latter aspect, for detection of a nucleic acid sequence which encodes the variant product in a biological sample, comprises the steps of:

(a) providing a probe comprising at least one of the nucleic acid sequences defined above;

(b) contacting the biological sample with said probe under conditions allowing hybridization of nucleic acid sequences thereby enabling formation of hybridization complexes;

(c) detecting hybridization complexes, wherein the presence of the complexes indicates the presence of nucleic acid sequence encoding the variant product in the biological sample.

The method as described above is qualitative, i.e. indicates whether the transcript is present in or absent from the sample. The method can also be quantitative, by determining the level of hybridization complexes and then calibrating said levels to determining levels of transcripts of the desired variant in the sample.

Both qualitative and quantitative determination methods can be used for diagnostic, prognostic and therapy planning purposes, especially in conjunction with cancer diseases. In addition qualitative determination may be indicative of the cancer stage.

By a preferred embodiment the probe is part of a nucleic acid chip used for detection purposes, i.e. the probe is a part of an array of probes each present in a known location on a solid support.

The nucleic acid sequence used in the above method may be a DNA sequence an RNA sequence, etc; it may be a coding or a sequence or a sequence complementary thereto (for respective detection of RNA transcripts or coding-DNA sequences). By quantization of the level of hybridization complexes

and calibrating the quantified results it is possible also to detect the level of the transcript in the sample.

Methods for detecting mutations in the region coding for the variant product are also provided, which may be methods carried-out in a binary fashion, namely merely detecting whether there is any mismatches between the normal variant nucleic acid sequence of the invention and the one present in the sample, or carried-out by specifically detecting the nature and location of the mutation. Detection of mutations may be of importance in the determination of predisposition to cancer, as well as in attempts to establish the prognosis of the cancer disease.

The present invention also concerns a method for detecting variant product in a biological sample, comprising the steps of:

(a) contacting with said biological sample the antibody of the invention, thereby forming an antibody-antigen complex; and

(b) detecting said antibody-antigen complex

wherein the presence of said antibody-antigen complex correlates with the presence of variant product in said biological sample.

Many diseases are diagnosed by detecting the presence of antibodies against a protein characterizing the disease in the blood, serum or any other body fluid of the patient. The present invention also concerns a method for detecting anti-variant antibody in a biological sample, comprising:

(a) contacting said sample with the variant product of the invention, thereby forming an antibody-antigen complex; and

(b) detecting said antibody-antigen complex

wherein the presence of said antibody-antigen complex correlates with the presence of anti-variant antibody in the sample.

As indicated above, both methods (for detection of variant product and for detection of the anti-variant antibody) can be quantitized to determine the level or the amount of the variant or antibody in the sample, alone or in comparison to the level of the original amino acid tumor-involved sequence from which it was varied or compared to the level of antibodies against the original amino acid sequence,

and qualitative and quantitative results may be used for diagnostic, prognostic and therapy planning purposes.

The invention also concerns distinguishing antibodies, i.e. antibodies capable of binding either to the variant product or to the original tumor-involved gene sequence from which the variant has been varied, while not binding to the original sequence or the variant product respectively. These distinguishing antibodies may be used for detection purposes.

By yet another aspect the invention also provides a method for identifying candidate compounds capable of binding to the variant product and modulating its activity (being either activators or deactivators). The method includes:

(i) providing a protein or polypeptide comprising an amino acid sequence substantially as depicted in any one of SEQ ID NO: 37 to 72, or a fragment of such a sequence;

(ii) contacting a candidate compound with said amino acid sequence;

(iii) measuring the physiological effect of said candidate compound on the activity of the amino acid sequences and selecting those compounds which show a significant effect on said physiological activity.

The present invention also concerns compounds identified by the above methods described above, which compound may either be an activator of the variant product or a deactivator thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, a preferred embodiment will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 is a comparison between the amino acid sequence of SEQ ID NO: 37 and the original tumor-involved sequence from which it has been varied;

Fig. 2 is a comparison between the amino acid sequence of SEQ ID NO: 38 and the original tumor-involved sequence from which it has been varied;

Fig. 3 is a comparison between the amino acid sequence of SEQ ID NO: 39 and the original tumor-involved sequence from which it has been varied;

Fig. 4 is a comparison between the amino acid sequence of SEQ ID NO: 40 and the original tumor-involved sequence from which it has been varied;

Fig. 5 is a comparison between the amino acid sequence of SEQ ID NO: 41 and the original tumor-involved sequence from which it has been varied;

Fig. 6 is a comparison between the amino acid sequence of SEQ ID NO: 42 and the original tumor-involved sequence from which it has been varied;

Fig. 7 is a comparison between the amino acid sequence of SEQ ID NO: 43 and the original tumor-involved sequence from which it has been varied;

Fig. 8 is a comparison between the amino acid sequence of SEQ ID NO: 44 and the original tumor-involved sequence from which it has been varied;

Fig. 9 is a comparison between the amino acid sequence of SEQ ID NO: 45 and the original tumor-involved sequence from which it has been varied;

Fig. 10 is a comparison between the amino acid sequence of SEQ ID NO: 46 and the original tumor-involved sequence from which it has been varied;

Fig. 11 is a comparison between the amino acid sequence of SEQ ID NO: 47 and the original tumor-involved sequence from which it has been varied;

Fig. 12 is a comparison between the amino acid sequence of SEQ ID NO: 48 and the original tumor-involved sequence from which it has been varied;

Fig. 13 is a comparison between the amino acid sequence of SEQ ID NO: 49 and the original tumor-involved sequence from which it has been varied;

Fig. 14 is a comparison between the amino acid sequence of SEQ ID NO: 50 and the original tumor-involved sequence from which it has been varied;

Fig. 15 is a comparison between the amino acid sequence of SEQ ID NO: 51 and the original tumor-involved sequence from which it has been varied;

Fig. 16 is a comparison between the amino acid sequence of SEQ ID NO: 52 and the original tumor-involved sequence from which it has been varied;

Fig. 17 is a comparison between the amino acid sequence of SEQ ID NO: 53 and the original tumor-involved sequence from which it has been varied;

Fig. 18 is a comparison between the amino acid sequence of SEQ ID NO: 54 and the original tumor-involved sequence from which it has been varied;

Fig. 19 is a comparison between the amino acid sequence of SEQ ID NO: 55 and the original tumor-involved sequence from which it has been varied;

Fig. 20 is a comparison between the amino acid sequence of SEQ ID NO: 56 and the original tumor-involved sequence from which it has been varied;

Fig. 21 is a comparison between the amino acid sequence of SEQ ID NO: 57 and the original tumor-involved sequence from which it has been varied;

Fig. 22 is a comparison between the amino acid sequence of SEQ ID NO: 58 and the original tumor-involved sequence from which it has been varied;

Fig. 23 is a comparison between the amino acid sequence of SEQ ID NO: 59 and the original tumor-involved sequence from which it has been varied;

Fig. 24 is a comparison between the amino acid sequence of SEQ ID NO: 60 and the original tumor-involved sequence from which it has been varied;

Fig. 25 is a comparison between the amino acid sequence of SEQ ID NO: 61 and the original tumor-involved sequence from which it has been varied;

Fig. 26 is a comparison between the amino acid sequence of SEQ ID NO: 62 and the original tumor-involved sequence from which it has been varied;

Fig. 27 is a comparison between the amino acid sequence of SEQ ID NO: 63 and the original tumor-involved sequence from which it has been varied;

Fig. 28 is a comparison between the amino acid sequence of SEQ ID NO: 64 and the original tumor-involved sequence from which it has been varied;

Fig. 29 is a comparison between the amino acid sequence of SEQ ID NO: 65 and the original tumor-involved sequence from which it has been varied;

Fig. 30 is a comparison between the amino acid sequence of SEQ ID NO: 66 and the original tumor-involved sequence from which it has been varied;

Fig. 31 is a comparison between the amino acid sequence of SEQ ID NO: 67 and the original tumor-involved sequence from which it has been varied;

Fig. 32 is a comparison between the amino acid sequence of SEQ ID NO: 68 and the original tumor-involved sequence from which it has been varied;

Fig. 33 is a comparison between the amino acid sequence of SEQ ID NO: 69 and the original tumor-involved sequence from which it has been varied;

Fig. 34 is a comparison between the amino acid sequence of SEQ ID NO: 70 and the original tumor-involved sequence from which it has been varied;

Fig. 35 is a comparison between the amino acid sequence of SEQ ID NO: 71 and the original tumor-involved sequence from which it has been varied;

Fig. 36 is a comparison between the amino acid sequence of SEQ ID NO: 72 and the original tumor-involved sequence from which it has been varied.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Example I: Comparison of variants with original sequences

Original sequences of tumor-involved genes were obtained from GenBank Version 115. Their tumor involvement was determined by comparison between the original sequences and the noval variant sequences was made using the BestFit application from the GCG suite version 10.0 (January 1999), with the defalut values:

Gap creation penalty (GapWeight): 50

Gap extension penalty (GapLengthWeight): 3

The comparison is shown in Fig. 1 to 34 which show the comparison of each of the variant products depicted in SEQ ID NO: 37 to 72 with the original tumor-involved sequence from which it was varied.

The following is a list which gives the name and the description of each original tumor-involved sequence from which the alternative splice variant has been varied by alternative splicing. The description is followed by the internal reference to the novel variant (NV-... etc.) and a short comparison between the variant and the original tumor-involved sequence. It should be noticed that several splice variants may have been originated from the same parent sequence by several different alternative splicings. The following table summarizes the accession number of the original sequence, the terminology of the new variant (NV-1 to

NV-34) and the description of the difference between the new variant and the original sequence.

Table

Accession	New variant #	Description of the new variant
KU70_HUMAN	NV-1	The new variant has an alternative 3' exon of 5 aa instead of 240 amino acids. It is probably missing the PHOSPHORYLATION (BY NUCLEAR KINASE NII) site and half of the PRO-RICH domain but retains the LEUCINE-ZIPPER domain.
KU70_HUMAN	NV-2	The new variant has a deletion of 210 aa between residues 304 – 515. Lacks the Pro-rich domain but retains the LEUCINE-ZIPPER domain and PHOSPHORYLATION (BY NUCLEAR KINASE NII) site.
LCK_HUMAN	NV-3	The new variant has an alternative 3' exon of 45 amino acids instead of 163 amino acids. The new variant retains both SH domains and most of the PROTEIN KINASE domain including two ATP BINDING sites and the ACTIVE SITE. It is missing the 3' end of the PROTEIN KINASE domain and lacks the AUTO-PHOSPHORYLATION and PHOSPHORYLATION sites.
LCK_HUMAN	NV-4	Insertion of 58 amino acids after amino acid 62 (insertion does not result in truncation). Insertion in first SH2 domain. The new variant retains all important sites including: the PROTEIN KINASE DOMAIN with two ATP BINDING sites, an ACTIVE SITE and an AUTO PHOSPHORYLATION site. An additional PHOSPHORYLATION site.

OSTP_HUMAN	NV-5	The new variant has an alternative 3' exon of 12 aa instead of 134 aa. The new variant maintains the CELL ATTACHMENT SITE and two GLYCOSILATION sites.
GA45_HUMAN	NV-6	The new variant has an alternative 5' exon of 72 amino acids instead of 125 amino acids. The new variant has a signal peptide and has the two PHOSPHORYLATION (BY CK2) sites.
WN11_HUMAN	NV-7	The new variant has a deletion of 22 amino acids after residue 312 (between 312-334). The new variant has all five potential GLYCOSILATION sites.
WN11_HUMAN	NV-8	The new variant has a deletion of 117 amino acids after residue 116 (between 116-233). The new variant is missing one potential GLYCOSILATION site (out of 5 sites).
KPCT_HUMAN	NV-9	The new variant has an alternative 3' exon of 3 amino acids instead of 94 amino acids. The alternative region is in the protein kinase domain. The new variant maintains the two PHORBOL-ESTER AND DAG BINDING domains, the two ATP binding sites and the active site of the kinase domain.
IRF1_HUMAN	NV-10	The new variant has an alternative 3' exon of 7 amino acids instead of 40 amino acids. The new variant maintains the DNA binding domain.
FGR1_HUMAN	NV-11	The new variant has an alternative 3' exon of 14 amino acids instead of 134 amino acids. The new variant has the entire extracellular domain and the TM, it is missing part of the cytoplasmic domain. The new variant

		maintains all 3 IMMUNO-GLOBULIN-LIKE DOMAINS, the protein KINASE domain, the ACTIVE site, and the 2 ATP binding sites, but it might be missing one of the two PHOSPHORYLATION (AUTO-) sites.
APE1_HUMAN	NV-12	The new variant has a gap of 22 amino acids between residues 146 – 169. The new variant maintains the active site and site important for substrate recognition.
APE1_HUMAN	NV-13	The new variant has an insertion of 25 amino acids after residue 18. The new variant maintains the active site and site important for substrate recognition.
MAD3_HUMAN	NV-14	The new variant has an alternative 3' exon of 3 amino acids instead of 15 amino acids. It retains all five ANK motifs and the two PHOSPHORYLATION sites.
MAD3_HUMAN	NV-15	The new variant has a deletion of 28 amino acids between 183 – 212. The deletion is in the ANK MOTIF 4. The new variant maintains 4 out of the five ANK MOTIFs and the two PHOSPHORYLATION sites.
EPA4_HUMAN	NV-16	Deletion of 65aa after residue 832 (832-898). Deletion in end of CYTOPLASMIC domain. The 3' end of the PROTEIN KINASE domain is missing, but all important sites are maintained. The new variant has two FYBRONECTIN TYPE III domains and the protein KINASE domain with 2 ATP binding sites, an ACTIVE site and an auto PHOSPHORYLATION site.

ETS2_HUMAN	NV-17	The new variant has a deletion of 26 aa between 87 - 114. The new variant maintains the DNA binding domain.
WN5A_HUMAN 1.	NV-18	The new variant has an alternative 3' exon of 4 amino acids instead of 109. It is identical to the known protein until residue 256. Two GLYCOSILATION sites out of four are missing in the new variant.
TYO3_HUMAN	NV-19	The new variant has an alternative 3' exon of 45 amino acids instead of 216 amino acids. The new variant is missing part of the PROTEIN KINASE domain and its AUTOPHOSPHORYLATION site. However, it maintains all other necessary domains: the ACTIVE site and the two ATP binding sites. The variant retains all 6 GLYCOSILATION sites, the 2 IG-like domains and the 2 FIBRONEXTIN TYPE III domains.
CAD2_HUMAN	NV-20	The new variant has an alternative 3' exon of 10 amino acids instead of 68 amino acids. The new variant maintains the extracellular domain and the TM domain. It is missing the end of the cytoplasmic domain and the SER-RICH domain. However, it has all other necessary domains including :5 CADHERIN REPEATS with 7 GLYCOSILATION sites.
MXI1_HUMAN	NV-21	NV_1 m85527_3 Insertion of 24aa after residue 79. Most likely truncated in insertion. Has basic DNA binding domain, but lacks helix-loop-helix.
MXI1_HUMAN	NV-22	NV_2 m85527_5 Alternative 5' exon. Identical to known from aa 26 to the end. Has a 5' exon of 31 aa versus 25 aa of the known. Has both DNA binding domain and

		helix loop helix. The alternative 5' exon bares a clathrin repeat. Supported by 4 ests.
MPK3_HUMAN	NV-23	Similar to known RNA at first 290 aa. Alternative 3' exon of 10 aa instead of 28 The new variant maintains the PROTEIN KINASE domain with its two ATP binding sites, the ACTIVE site and two POSPHORYLATION sites.
XRC1_HUMAN	NV-24	First 242aa identical to known RNA. Alternative short 3' exon of 50 aa Instead of 391aa.
XRC1_HUMAN	NV-25	Identical to known RNA in first 241 aa. Alternative 3' exon of 25 aa instead of 392.
XRC1_HUMAN	NV-26	Identical to known RNA in first 186 aa. Alternative short 3' exon of length 61 aa, instead of 447 aa.
XRC1_HUMAN	NV-27	Identical to known RNA in first 540 aa. Alternative 3' exon of 84 aa instead of 93 aa.
MERL_HUMAN	NV-28	Deletion of 29 aa from position 333. The new variant retains the Band 4-1 like domain. (Band 4.1, which links the spectrin-actin cytoskeleton of erythrocytes to the plasma membrane.)
DP1_HUMAN	NV-29	Alternative 3' exon of 21 amino acids instead of 72 amino acids. The new variant retains the two transmembrane domains.
MDR1_HUMAN	NV-30	Alternative exon at 3' end at cytoplasmic domain. 1 aa instead of 3 of the known. Identical to known until aa 1277.
MDR1_HUMAN	NV-31	The new variant is a truncated protein. It has an alternative 3' exon of 12 amino acids instead of 713. It is

		identical to the known protein until residue 567. The new variant retains only one out of two ATP binding sites, and six out of twelve TM domains. It has one out of three cytoplasmic domains and is truncated in the middle of the second cytoplasmic domain.
MK08_HUMAN	NV-32	Identical to known until aa 205. Truncated. Has additional 13 aa. Lacks part of the protein kinase domain. Retains the active site the two ATP binding sites and the two phosphorylation sites.
MK08_HUMAN	NV-33	Alternative 3' exon of 14 aa instead of 134 aa. Identical to known until residue 293. Lacks end of protein kinase domain. Retains the active site, the two ATP binding sites and the two phosphorylation sites.
MK08_HUMAN	NV-34	Alternative 3' exon of 7 aa instead of 95 aa. Identical to known until residue 332. Has entire protein kinase domain including the active site, the two ATP binding sites and the two phosphorylation sites.
MAPK12_HUMAN	NV-35	The new variant contains 152 N-terminal amino acids of the original protein. The new variant has alternative 25 amino acids in its C-terminus, instead of original 215 amino acids. It contains the NP_BIND (between the amino acids 33 – 41, and the ATP binding site at position 56. The truncated variant has only part of the kinase domain, it lacks the active site and both the phosphorylation sites that activates the kinase. . This truncated splice variant can act as dominant negative.
KPCT_HUMAN	NV-36	The new variant has an alternative 3' exon of 36 amino acids instead of 94 original amino acids. The alternative region is in the PROTEIN KINASE domain. The new variant maintains

		the two PHORBOL-ESTER AND DAG BINDING domains, the two ATP binding sites and the ACTIVE of the KINASE domain.

The following is a list of the original tumor-involved sequences, followed by all the splice variants obtained therefrom with a list of differences between the original TIG sequence and the variant.

KU (p70/p80)

KU70_HUMAN

FUNCTION: SINGLE STRANDED DNA-DEPENDENT ATP-DEPENDENT HELICASE. HAS A ROLE IN CHROMOSOME TRANSLOCATION. THE DNA HELICASE II COMPLEX BINDS PREFERENTIALLY TO FORK-LIKE ENDS OF DOUBLE-STRANDED DNA IN A CELL CYCLE-DEPENDENT MANNER. IT WORKS IN THE 3'-5' DIRECTION. BINDING TO DNA MAY BE MEDIATED BY P70.
SUBUNIT: HETERODIMER OF A 70 KD AND A 80 KD SUBUNIT.
SUBCELLULAR LOCATION: NUCLEAR.
PTM: PHOSPHORYLATED IN VIVO AT SERINE RESIDUES (BY SIMILARITY).
DISEASE: INDIVIDUALS WITH SLE AND RELATED DISORDERS PRODUCE EXTREMELY LARGE AMOUNTS OF AUTOANTIBODIES TO P70 AND P86. EXISTENCE OF A MAJOR AUTOANTIGENIC EPITOPE OR EPITOPES ON THE CARBOXY TERMINAL 190 AMINO ACIDS OF P70 CONTAINING THE LEUCINE REPEAT. THE MAJORITY OF AUTOANTIBODIES TO P70 IN MOST SERA FROM PATIENTS WITH SLE SEEM TO BE REACTIVE WITH THIS REGION.
SIMILARITY: BELONGS TO THE ATP-DEPENDENT DNA HELICASE II 70 KD SUBUNIT FAMILY.

NV_1

The new variant has an alternative 3' exon of 5 amino acids instead of 240 amino acids. It is probably missing the PHOSPHORYLATION (BY NUCLEAR

KINASE NII) site and half of the PRO-RICH domain but retains the LEUCINE-ZIPPER domain.

KU (p70/p80)

KU70_HUMAN

NV_2

The new variant has a deletion of 210 amino acids between residues 304 – 515. The new variant lacks the PRO-RICH domain but retains the LEUCINE-ZIPPER domain and PHOSPHORYLATION (BY NUCLEAR KINASE NII) site.

LCK

LCK_HUMAN

PROTO-ONCOGENE TYROSINE-PROTEIN KINASE LCK
<u>FUNCTION</u>: MAY PARTICIPATE IN ANTIGEN-INDUCED T-CELL ACTIVATION.
<u>CATALYTIC ACTIVITY</u>: ATP + A PROTEIN TYROSINE = ADP + PROTEIN TYROSINE PHOSPHATE.
<u>ENZYME REGULATION</u>: REGULATED BY PHOSPHORYLATION ON TYR-504.
<u>SUBCELLULAR LOCATION</u>: BOUND TO THE CYTOPLASMIC DOMAIN OF EITHER CD4 OR CD8.
<u>SIMILARITY</u>: CONTAINS 1 SH2 DOMAIN.
<u>SIMILARITY</u>: CONTAINS 1 SH3 DOMAIN.
<u>SIMILARITY</u>: TO OTHER PROTEIN-TYROSINE KINASES IN THE CATALYTIC DOMAIN. BELONGS TO THE SRC SUBFAMILY.

NV_3

The new variant has an alternative 3' exon of 45 amino acids instead of 163 amino acids. The new variant retains both SH domains and most of the PROTEIN KINASE domain including two ATP BINDING sites and the

ACTIVE SITE. It is missing the 3' end of the PROTEIN KINASE domain and lacks the AUTO-PHOSPHORYLATION and PHOSPHORYLATION sites.

LCK

LCK_HUMAN

NV_4

Insertion of 58 amino acids after amino acid 62 (insertion does not result in truncation). Insertion in first SH2 domain. The new variant retains all important sites including: the PROTEIN KINASE DOMAIN with two ATP BINDING sites, an ACTIVE SITE and an AUTO PHOSPHORYLATION site. An additional PHOSPHORYLATION site.

OSTEOPONTIN

OSTP_HUMAN

<u>FUNCTION</u>: BINDS TIGHTLY TO HYDROXYAPATITE. APPEARS TO FORM AN INTEGRAL PART OF THE MINERALIZED MATRIX. PROBABLY IMPORTANT TO CELL-MATRIX INTERACTION.
<u>ALTERNATIVE PRODUCTS</u>: TWO ISOFORMS; OP1A AND OP1B (SHOWN HERE); ARE PRODUCES BY ALTERNATIVE SPLICING.
<u>PTM</u>: EXTENSIVELY PHOSPHORYLATED ON SERINE RESIDUES.
<u>PTM</u>: N- AND O-GLYCOSYLATED.
<u>DISEASE</u>: THIS PROTEIN PLAYS A PRINCIPAL ROLE IN URINARY STONE FORMATION AS THE STONE MATRIX

NV_5

The new variant has an alternative 3' exon of 12 amino acids instead of 134 amino acids. The new variant maintains the CELL ATTACHMENT SITE and two GLYCOSILATION sites.

GADD45

GA45_HUMAN

GROWTH ARREST AND DNA-DAMAGE-INDUCIBLE PROTEIN
FUNCTION: INVOLVED IN THE REGULATION OF GROWTH AND APOPTOSIS. MEDIATES ACTIVATION OF STRESS-RESPONSIVE MTK1/MEKK4 MAPKKK.
SIMILARITY: BELONGS TO THE GADD45 / MYD118 FAMILY.

NV_6

The new variant has an alternative 5' exon of 72 amino acids instead of 125 amino acids. The new variant has a signal peptide and has the two PHOSPHORYLATION (BY CK2) sites.

WNT-11 PROTEIN

WN11_HUMAN

FUNCTION: PROBABLE DEVELOPMENTAL PROTEIN. MAY BE A SIGNALING MOLECULE WHICH AFFECT THE DEVELOPMENT OF DISCRETE REGIONS OF TISSUES. IS LIKELY TO SIGNAL OVER ONLY FEW CELL
DIAMETERS.
SUBCELLULAR LOCATION: POSSIBLY SECRETED AND ASSOCIATES WITH THE EXTRACELLULAR MATRIX.
SIMILARITY: BELONGS TO THE WNT FAMILY

NV_7

The new variant has a deletion of 22 amino acids after residue 312 (between 312-334). The new variant has all five potential GLYCOSILATION sites.

WNT-11 PROTEIN

WN11_HUMAN

NV_8

The new variant has a deletion of 117 amino acids after residue 116 (between 116-233). The new variant is missing one potential GLYCOSILATION site (out of 5 sites).

PROTEIN KINASE C, THETA TYPE

KPCT_HUMAN

FUNCTION: THIS IS CALCIUM-INDEPENDENT, PHOSPHOLIPID-DEPENDENT, SERINE- AND THREONINE-SPECIFIC ENZYME.
FUNCTION: PKC IS ACTIVATED BY DIACYLGLYCEROL WHICH IN TURN PHOSPHORYLATES A RANGE OF CELLULAR PROTEINS. PKC ALSO SERVES AS THE RECEPTOR FOR PHORBOL ESTERS, A CLASS OF TUMOR
PROMOTERS.
TISSUE SPECIFICITY: SKELETAL MUSCLE, MEGAKARYOBLASTIC CELLS AND PLATELETS.
SIMILARITY: CONTAINS 2 ZINC-DEPENDENT PHORBOL-ESTER AND DAG BINDING DOMAINS.
SIMILARITY: BELONGS TO THE SER/THR FAMILY OF PROTEIN KINASES. PKC SUBFAMILY.

NV_9

The new variant has an alternative 3' exon of 3 amino acids instead of 94 amino acids. The alternative region is in the PROTEIN KINASE domain. The new variant maintains the two PHORBOL-ESTER AND DAG BINDING domains, the two ATP binding sites and the ACTIVE of the KINASE domain.

INTERFERON REGULATORY FACTOR 1

IRF1_HUMAN

FUNCTION: SPECIFICALLY BINDS TO THE UPSTREAM REGULATORY REGION OF TYPE I IFN AND IFN-INDUCIBLE MHC CLASS I GENES (THE INTERFERON CONSENSUS SEQUENCE (ICS)) AND ACTIVATES THOSE GENES.
SUBCELLULAR LOCATION: NUCLEAR.
INDUCTION: BY VIRUSES AND IFN.
DISEASE: DELETION OR REARRANGEMENT OF IRF1 ARE A CAUSE OF PRELEUKEMIC MYELODYSPLASTIC SYNDROME (MDS) AND OF ACUTE MYELOGENOUS LEUKEMIA (AML).
SIMILARITY: BELONGS TO THE IRF FAMILY.

NV_10

The new variant has an alternative 3' exon of 7 amino acids instead of 40 amino acids. The new variant maintains the DNA binding domain.

BASIC FIBROBLAST GROWTH FACTOR RECEPTOR 1

FGR1_HUMAN

FUNCTION: RECEPTOR FOR BASIC FIBROBLAST GROWTH FACTOR. A SHORTER FORM OF THE RECEPTOR COULD BE A RECEPTOR FOR ACIDIC FGF (AFGF).
CATALYTIC ACTIVITY: ATP + PROTEIN TYROSINE = ADP + PROTEIN TYROSINE PHOSPHATE.
SUBCELLULAR LOCATION: TYPE I MEMBRANE PROTEIN.
ALTERNATIVE PRODUCTS: MANY FORMS OF FGFR1 ARE PRODUCED BY ALTERNATIVE SPLICING. THE FORM SHOWN HERE IS KNOWN AS ALPHA-A1.
DISEASE: DEFECTS IN FGFR1 ARE ONE OF THE CAUSES OF PFEIFFER SYNDROME, ALSO CALLED ACROCEPHALOSYNDACTYLY TYPE V (ACS V), CHARACTERIZED BY CRANIOSYNOSTOSIS (PREMATURE FUSION OF THE SKULL SUTURES) WITH DEVIATION AND ENLARGEMENT OF THE THUMBS AND GREAT

TOES,BRACHYMESOPHALANGY, WITH PHALANGEAL ANKYLOSIS AND A VARYING DEGREE OF SOFT TISSUE SYNDACTYLY.
SIMILARITY: BELONGS TO THE FIBROBLAST GROWTH FACTOR RECEPTOR FAMILY.
SIMILARITY: CONTAINS 3 IMMUNOGLOBULIN-LIKE DOMAINS.

NV_11

The new variant has an alternative 3' exon of 14 amino acids instead of 134 amino acids. The new variant has the entire extracellular domain and the TM, it is missing part of the cytoplasmic domain. The new variant maintains all 3 IMMUNOGLOBULIN-LIKE DOMAINS, the protein KINASE domain, the ACTIVE site, and the 2 ATP binding sites, but it might be missing one of the two PHOSPHORYLATION (AUTO-) sites.

REF-1 PROTEIN DNA-(APURINIC OR APYRIMIDINIC SITE) LYASE APE1_HUMAN

FUNCTION: REPAIRS OXIDATIVE DNA DAMAGES IN VITRO. MAY HAVE A ROLE IN PROTECTION AGAINST CELL LETHALITY AND SUPPRESSION OF MUTATIONS. REMOVES THE BLOCKING GROUPS FROM THE 3'
TERMINI OF THE DNA STRAND BREAKS GENERATED BY IONIZING RADIATIONS AND BLEOMYCIN.
CATALYTIC ACTIVITY: ENDONUCLEOLYTIC CLEAVAGE NEAR APURINIC OR APYRIMIDINIC SITES TO PRODUCTS WITH 5'-PHOSPHATE.
SUBCELLULAR LOCATION: NUCLEAR.
SIMILARITY: BELONGS TO THE AP/EXOA FAMILY OF DNA REPAIR ENZYMES.

NV_12

The new variant has a gap of 22 amino acids between residues 146 – 169. The new variant maintains the ACTIVE site and site important for substrate recognition.

NV_13

The new variant has an insertion of 25 amino acids after residue 18.It maintains the ACTIVE site and the site important for substrate recognition.

MAD3 MAJOR HISTOCOMPATIBILITY COMPLEX ENHANCER-BINDING PROTEIN

MAD3_HUMAN

FUNCTION: I-KAPPA-B-LIKE ACTIVITY. MAY BE INVOLVED IN REGULATION OF TRANSCRIPTIONAL RESPONSES TO NF-KAPPA-B, INCLUDING ADHESION- DEPENDENT PATHWAYS OF MONOCYTE ACTIVATION. INTERACTS DIRECTLY WITH THE NF-KAPPA-B COMPLEX, PRESUMABLY THROUGH THE P65 SUBUNIT.
INDUCTION: INDUCED IN ADHERENT MONOCYTES.
PTM: PHOSPHORYLATION OF I-KAPPA-B BLOCKS ITS ABILITY TO INHIBIT NF-KAPPA-B DNA-BINDING ACTIVITY.
SIMILARITY: CONTAINS 5 ANK REPEATS.

NV_14

The new variant has an alternative 3' exon of 3 amino acids instead of 15 amino acids. It retains all five ANK motifs and the two PHOSPHORYLATION sites.

NV_15

The new variant has a deletion of 28 amino acids between 183 – 212. The deletion is in the ANK MOTIF 4.The new variant maintains 4 out of the five ANK MOTIFs and the two PHORYLATION sites.

RECEPTOR PROTEIN-TYROSINE KINASE HEK8

EPA4_HUMAN

FUNCTION: RECEPTOR FOR MEMBERS OF THE EPHRIN-A FAMILY. BINDS TO EPHRIN-A1, -A4 AND -A5. BINDS MORE POORLY TO EPHRIN-A2 AND A-3.
CATALYTIC ACTIVITY: ATP + A PROTEIN TYROSINE = ADP + PROTEIN TYROSINE PHOSPHATE.
SUBCELLULAR LOCATION: TYPE I MEMBRANE PROTEIN.
SIMILARITY: CONTAINS 2 FIBRONECTIN TYPE III-LIKE DOMAINS.
SIMILARITY: TO OTHER PROTEIN-TYROSINE KINASES IN THE CATALYTIC DOMAIN. BELONGS TO THE EPHRIN RECEPTOR FAMILY.

NV_16

Deletion of 65 amino acids between 832 – 898. The deletion in the cytoplasmic domain. The 3' end of the PROTEIN KINASE domain is missing, but all important sites are maintained. The new variant has two FYBRONECTIN TYPE III domains and the protein KINASE domain with 2 ATP binding sites, an ACTIVE site and an auto PHOSPHORYLATION site.

C-ETS-2 PROTEIN

ETS2_HUMAN

SUBCELLULAR LOCATION: NUCLEAR.
SIMILARITY: BELONGS TO THE ETS FAMILY.

NV_17

The new variant has a deletion of 26 amino acids between 87 – 114. The new variant maintains the DNA binding domain.

WNT-5A PROTEIN

WN5A_HUMAN

FUNCTION: PROBABLE DEVELOPMENTAL PROTEIN. MAY BE A SIGNALING MOLECULE WHICH AFFECTS THE DEVELOPMENT OF DISCRETE REGIONS OF TISSUES. IS LIKELY TO SIGNAL OVER ONLY FEW CELL DIAMETERS.

SUBCELLULAR LOCATION: POSSIBLY SECRETED AND ASSOCIATES WITH THE EXTRACELLULAR MATRIX.

SIMILARITY: BELONGS TO THE WNT FAMILY

NV_18

The new variant has an alternative 3' exon of 4 amino acids instead of 109. It is identical to the known protein until residue 256. Two GLYCOSILATION sites out of four are missing in the new variant.

TYROSINE-PROTEIN KINASE SKY

TYO3_HUMAN

FUNCTION: MAY BE INVOLVED IN CELL ADHESION PROCESSES, PARTICULARLY IN THE CENTRAL NERVOUS SYSTEM.

SUBCELLULAR LOCATION: TYPE I MEMBRANE PROTEIN.

TISSUE SPECIFICITY: ABUNDANT IN THE BRAIN AND LOWER LEVELS IN OTHER TISSUES.

SIMILARITY: TO OTHER PROTEIN-TYROSINE KINASES IN THE CATALYTIC DOMAIN.

SIMILARITY: CONTAINS 2 IMMUNOGLOBULIN-LIKE C2-TYPE DOMAINS.

SIMILARITY: CONTAINS 2 FIBRONECTIN TYPE III-LIKE DOMAINS.

NV_19

The new variant has an alternative 3' exon of 45 amino acids instead of 216 amino acids. The new variant is missing part of the PROTEIN KINASE domain and its AUTOPHOSPHORYLATION site. However, it maintains all other necessary domains: the ACTIVE site and the two ATP binding sites. The variant retains all 6 GLYCOSILATION sites, the 2 IG-like domains and the 2 FIBRONEXTIN TYPE III domains.

NEURAL-CADHERIN
CAD2_HUMAN

<u>FUNCTION</u>: CADHERINS ARE CALCIUM DEPENDENT CELL ADHESION PROTEINS. THEY PREFERENTIALLY INTERACT WITH THEMSELVES IN A HOMOPHILIC MANNER IN CONNECTING CELLS; CADHERINS MAY THUS CONTRIBUTE TO THE SORTING OF HETEROGENEOUS CELL TYPES. N-CADHERIN MAY BE INVOLVED IN NEURONAL RECOGNITION MECHANISM.
<u>SUBCELLULAR LOCATION</u>: TYPE I MEMBRANE PROTEIN.
<u>SIMILARITY</u>: BELONGS TO THE CADHERIN FAMILY.

NV_20

The new variant has an alternative 3' exon of 10 amino acids instead of 68 amino acids. The new variant maintains the extracellular domain and the TM domain. It is missing the end of the cytoplasmic domain and the SER-RICH domain. However, it has all other necessary domains including: 5 CADHERIN REPEATS with 7 GLYCOSILATION sites.

MXI1 MAX INTERACTING PROTEIN 1
MXI1_HUMAN

<u>FUNCTION</u>: TRANSCRIPTIONAL REPRESSOR. MXI1 BINDS WITH MAX TO FORM A SEQUENCE-SPECIFIC DNA-BINDING PROTEIN COMPLEX

WHICH RECOGNIZES THE CORE SEQUENCE 5'-CAC[GA]TG-3'. MXI1 THUS ANTAGONIZES MYC TRANSCRIPTIONAL ACTIVITY BY COMPETING FOR MAX.

SUBUNIT: EFFICIENT DNA BINDING REQUIRES DIMERIZATION WITH ANOTHER BHLH PROTEIN.BINDS DNA AS A HETERODIMER WITH MAX.

SUBCELLULAR LOCATION: NUCLEAR.

TISSUE SPECIFICITY: HIGH LEVELS FOUND IN THE BRAIN, HEART AND LUNG WHILE LOWER LEVELS ARE SEEN IN THE LIVER, KIDNEY AND SKELETAL MUSCLE.

DISEASE: DEFECTS IN MXI1 ARE FOUND IN SOME PATIENTS WITH PROSTATE TUMORS.

SIMILARITY: BELONGS TO THE BASIC HELIX-LOOP-HELIX (BHLH) FAMILY OF TRANSCRIPTION FACTORS.

NV_21

The new variant has an insertion of 24 amino acids after residue 79. It is most likely truncated within the insertion. The new variant retains the BASIC DNA BINDING domain, but lacks the HELIX LOOP HELIX motif.

MXI1 MAX INTERACTING PROTEIN 1

MXI1_HUMAN

NV_22

The new variant has an alternative 5' exon of 31 amino acids instead of 25. It is identical to the known protein from residue 26 to the end. The new variant has both the DNA BINDING DOMAIN and the HELIX LOOP HELIX motif. The alternative 5' exon bares a clathrin repeat.

DUAL SPECIFICITY MITOGEN-ACTIVATED PROTEIN KINASE KINASE 3

MPK3_HUMAN

FUNCTION: DUAL SPECIFICITY KINASE. IS ACTIVATED BY CYTOKINES AND ENVIRONMENTAL STRESS IN VIVO. CATALYZES THE CONCOMITANT PHOSPHORYLATION OF A THREONINE AND A TYROSINE RESIDUE IN THE MAP KINASE P38.
ENZYME REGULATION: ACTIVATED BY DUAL PHOSPHORYLATION ON SER-189 AND THR-193.
TISSUE SPECIFICITY: ABUNDANT EXPRESSION IS SEEN IN THE SKELETAL MUSCLE. IT IS ALSO WIDELY EXPRESSED IN OTHER TISSUES.
PTM: AUTOPHOSPHORYLATED.
SIMILARITY: BELONGS TO THE SER/THR FAMILY OF PROTEIN KINASES. MAP KINASE KINASE SUBFAMILY.

NV_23

The new variant has an alternative 3' exon of 10 amino acids instead of 28 amino acids. The new variant maintains the PROTEIN KINASE domain with its two ATP binding sites, the ACTIVE site and two POSPHORYLATION sites.It may lack a few amino acids at the end of the PROTEIN KINASE domain.

DNA-REPAIR PROTEIN XRCC1

XRC1_HUMAN

FUNCTION: CORRECTS DEFECTIVE DNA STRAND-BREAK REPAIR AND SISTER CHROMATID EXCHANGE FOLLOWING TREATMENT WITH IONIZING RADIATION AND ALKYLATING AGENTS.
SUBCELLULAR LOCATION: NUCLEAR (PROBABLE).
SIMILARITY: SOME, TO S.POMBE RAD4/CUT5.

NV_24

Alternative 3' exon of 50 amino acids instead of 391 amino acids.

DNA-REPAIR PROTEIN XRCC1

XRC1_HUMAN

NV_25

Alternative 3' exon of 25 amino acids instead of 392 amino acids.

DNA-REPAIR PROTEIN XRCC1

XRC1_HUMAN

NV_26

Alternative 3' exon of 61 amino acids instead of 447 amino acids.

DNA-REPAIR PROTEIN XRCC1

XRC1_HUMAN

NV_27

Alternative 3' exon of 84 amino acids instead of 93 amino acids.

MERLIN SCHWANNOMIN (NF2)

MERL_HUMAN

FUNCTION: PROBABLY ACTS AS A MEMBRANE STABILIZING PROTEIN.

TISSUE SPECIFICITY: IN FETAL BRAIN; IN KIDNEY, LUNG, BREAST, AND OVARY.

DISEASE: NEUROFIBROMATOSIS 2 (NF2) OR CENTRAL NEUROFIBROMATOSIS IS A GENETIC DISORDER CHARACTERIZED BY BILATERAL VESTIBULAR SCHWANNOMAS (FORMERLY CALLED

ACOUSTIC NEUROMAS), SCHWANNOMAS OF OTHER CRANIAL AND PERIPHERAL NERVES,MENINGIOMAS, AND EPENDYMOMAS. IT IS INHERITED IN AN AUTOSOMAL DOMINANT FASHION WITH FULL PENETRANCE. AFFECTED INDIVIDUALS GENERALLY DEVELOP SYMPTOMS OF EIGHTH-NERVE DYSFUNCTION IN EARLY ADULTHOOD, INCLUDING DEAFNESS AND BALANCE DISORDER. ALTHOUGH THE TUMORS OF NF2 ARE HISTOLOGICALLY BENIGN, THEIR ANATOMIC LOCATION MAKES MANAGEMENT DIFFICULT, AND PATIENTS SUFFER GREAT MORBIDITY AND MORTALITY.
SIMILARITY: CONTAINS A DOMAIN FOUND IN BAND 4.1, EZRIN, MOESIN, RADIXIN, AND TALIN.

NV_28

The new variant has a deletion of 29 amino acids after residue 333.The new variant maintains the BAND 4,1 – LIKE domain. (Band 4.1, which links the spectrin-actin cytoskeleton of erythrocytes to the plasma membrane).

DP1 POLYPOSIS LOCUS PROTEIN 1

DP1_HUMAN

SUBCELLULAR LOCATION: INTEGRAL MEMBRANE PROTEIN (POTENTIAL).
SIMILARITY: TO C.ELEGANS T19C3.4.

NV_29

Alternative 3' exon of 21 amino acids instead of 72 amino acids. The new variant maintains the two transmembrane domains.

MDR1 MULTIDRUG RESISTANCE PROTEIN 1

MDR1_HUMAN

FUNCTION: ENERGY-DEPENDENT EFFLUX PUMP RESPONSIBLE FOR DECREASED DRUG ACCUMULATION IN MULTIDRUG-RESISTANT CELLS.
SUBCELLULAR LOCATION: INTEGRAL MEMBRANE PROTEIN.
SIMILARITY: BELONGS TO THE ATP-BINDING TRANSPORT PROTEIN FAMILY (ABC TRANSPORTERS). MDR SUBFAMILY.

NV_30

The new variant has an alternative 3' exon of 1 amino acid, instead of 3 of the known protein. The new variant is identical to the known protein until residue 1277. It maintains all important sites.

MDR1 MULTIDRUG RESISTANCE PROTEIN 1

MDR1_HUMAN

NV_31

The new variant is a truncated protein. It has an alternative 3' exon of 12 amino acids instead of 713. It is identical to the known protein until residue 567. The new variant retains only one out of two ATP binding sites, and six out of twelve TM domains. It has one out of three cytoplasmic domains and is truncated in the middle of the second cytoplasmic domain.

JNK1 – MITOGEN ACTIVATED PROTEIN KINASE 8

MK08_HUMAN

FUNCTION: PROBABLY PLAYS A ROLE IN THE SIGNAL TRANSDUCTION PATHWAY INITIATED BY PROINFLAMMATORY CYTOKINES AND UV RADIATION. BINDS TO THE N-TERMINAL ACTIVATION DOMAINS OF C-JUN AND ATF2 AND PHOSPHORYLATES

THEIR REGULATORY SITES (RESPECTIVELY SER-63 AND SER-73; THR-69 AND THR-71). JNK1 ISOFORMS DISPLAY DIFFERENT BINDING PATTERNS: BETA-1 PREFERENTIALLY BINDS TO C-JUN, WHEREAS ALPHA-1, ALPHA-2, AND BETA-2 HAVE A SIMILAR LOW LEVEL OF BINDING TO BOTH C-JUN OR ATF2. HOWEVER THERE IS NO CORRELATION BETWEEN BINDING AND PHOSPHORYLATION, WHICH IS ACHIEVED ABOUT AT THE SAME EFFICIENCY BY ALL ISOFORMS.
ENZYME REGULATION: ACTIVATED BY THREONINE AND TYROSINE PHOSPHORYLATION.
ALTERNATIVE PRODUCTS: FOUR ISOFORMS JNK1 ALPHA-1, JNK1 ALPHA-2 (SHOWN HERE), JNK1 BETA-1, AND JNK1 BETA-2 ARE PRODUCED BY ALTERNATIVE SPLICING.
INDUCTION: BY UV LIGHT, INTERLEUKIN-1 AND BY HA-RAS.
SIMILARITY: BELONGS TO THE CDC2/CDC28 SUBFAMILY OF SER/THR PROTEIN KINASES. STRONGEST SIMILARITY WITH OTHER MAP KINASES.

NV_32

The new variant is a truncated protein. It has an alternative 3' exon of 13 amino acids instead of 222 amino acids. It is identical to the known protein until residue 205. The new variant lacks part of the PROTEIN KINASE domain, however it retains the ACTIVE SITE, the two ATP binding sites and the two PHOSPHORYLATION sites.

JNK1 – MITOGEN ACTIVATED PROTEIN KINASE 8
MK08_HUMAN

NV_33

The new variant has an alternative 3' exon of 14 amino acids instead of 134 amino acids of the known protein. It is identical to the known protein until residue 293. The new variant lacks the end of the PROTEIN KINASE domain, but retains the ACTIVE SITE, the two ATP binding sites and the two PHOSPHORYLATION sites.

JNK1 – MITOGEN ACTIVATED PROTEIN KINASE 8
MK08_HUMAN

NV_34

The new variant has an alternative 3' exon of 7 amino acids a instead of 95 amino acids. It is identical to the known protein until residue 332. Has the entire PROTEIN KINASE domain including the ACTIVE SITE, the two ATP binding sites and the two PHOSPHORYLATION sites.

MITOGEN-ACTIVATED PROTEIN KINASE 12

Synonym(s) EC 2.7.1- extracellular signal-regulated kinase 6 EC 2.7.1- ERK 6 ERK 5 stress-activated protein kinase-3 mitogen-activated protein kinase P38 gamma map kinase P38 gamma

Gene name(s) MAPK12 or ERK 6 or SAPK 3

<u>FUNCTION</u>: PHOSPHORYLATES MYELIN BASIC PROTEIN (MBP); ACTS AS SIGNAL TRANSDUCER DURING THE DIFFERENTIATION OF MYOBLASTS TO MYOTUBES. OVEREXPRESSION ENHANCES THIS DIFFERENTIATION EVENT, WHEREAS INACTIVATION EXHIBITS IT AND MAINTAINS THE CELLS IN A PROLIFERATIVE STATE.
<u>ENZYME REGULATION</u>: ACTIVATED BY PHSOPHORYLATION ON THREONINE AND TYROSINE (BY SIMILARITY).
<u>TISSUE SPECIFICITY</u>: HIGHLY EXPRESSED IN SKELETAL MUSCLE.
<u>SIMILARITY</u>: BELONGS TO THE SER/THR FAMILY OF PROTEIN KINASES. MAP KINASE FAMILY.

NV_35

The new variant contains 152 N-terminal amino acids of the original protein. The new variant has alternative 25 amino acids in its C-terminus, instead of original 215 amino acids. It contains the NP_BIND (between the amino acids 33 – 41, and the ATP binding site at position 56. The truncated variant has only part of the kinase domain, it lacks the active site and both the phosphorylation sites that activates the kinase. This truncated splice variant can act as dominant negative.

PROTEIN KINASE C, THETA TYPE
KPCT_HUMAN

FUNCTION: THIS IS CALCIUM-INDEPENDENT, PHOSPHOLIPID-DEPENDENT, SERINE- AND THREONINE-SPECIFIC ENZYME.
FUNCTION: PKC IS ACTIVATED BY DIACYLGLYCEROL WHICH IN TURN PHOSPHORYLATES A RANGE OF CELLULAR PROTEINS. PKC ALSO SERVES AS THE RECEPTOR FOR PHORBOL ESTERS, A CLASS OF TUMOR PROMOTERS.
TISSUE SPECIFICITY: SKELETAL MUSCLE, MEGAKARYOBLASTIC CELLS AND PLATELETS.
SIMILARITY: CONTAINS 2 ZINC-DEPENDENT PHORBOL-ESTER AND DAG BINDING DOMAINS.
SIMILARITY: BELONGS TO THE SER/THR FAMILY OF PROTEIN KINASES. PCK SUBFAMILY.

NV_36

The new variant has an alternative 3′ exon of 36 amino acids instead of 94 original amino acids. The alternative region is in the PROTEIN KINASE domain. The new variant maintains the two PHORBOL-ESTER AND DAG BINDING domains, the two ATP binding sites and the ACTIVE of the KINASE domain.

Example II: Variant nucleic acid sequence

The nucleic acid sequences of the invention include nucleic acid sequences which encode variant product and fragments and analogs thereof. The nucleic acid sequences may alternatively be sequences complementary to the above coding sequence, or to a region of said coding sequence. The length of the complementary sequence is sufficient to avoid the expression of the coding sequence. The nucleic acid sequences may be in the form of RNA or in the form of DNA, and include messenger RNA, synthetic RNA and DNA, cDNA, and genomic DNA. The DNA may be double-stranded or single-stranded, and if single-stranded may be the coding strand or the non-coding (anti-sense, complementary) strand. The nucleic acid sequences may also both include dNTPs, rNTPs as well as non naturally occurring sequences. The sequence may also be a part of a hybrid between an amino acid sequence and a nucleic acid sequence.

In a general embodiment, the nucleic acid sequence has at least 90%, identity with any one of the sequence identified as SEQ ID NO: 1 to SEQ ID NO: 36 provided that this sequence is not completely identical with that of the original sequence.

The nucleic acid sequences may include the coding sequence by itself. By another alternative the coding region may be in combination with additional coding sequences, such as those coding for fusion protein or signal peptides, in combination with non-coding sequences, such as introns and control elements, promoter and terminator elements or 5' and/or 3' untranslated regions, effective for expression of the coding sequence in a suitable host, and/or in a vector or host environment in which the variant nucleic acid sequence is introduced as a heterologous sequence.

The nucleic acid sequences of the present invention may also have the product coding sequence fused in-frame to a marker sequence which allows for purification of the variant product. The marker sequence may be, for example, a

hexahistidine tag to provide for purification of the mature polypeptide fused to the marker in the case of a bacterial host, or, the marker sequence may be a hemagglutinin (HA) tag when a mammalian host, e.g. COS-7 cells, is used. The HA tag corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson, I., *et al. Cell* 37:767 (1984)).

Also included in the scope of the invention are fragments as defined above also referred to herein as oligonucleotides, typically having at least 20 bases, preferably 20-30 bases corresponding to a region of the coding-sequence nucleic acid sequence. The fragments may be used as probes, primers, and when complementary also as antisense agents, and the like, according to known methods.

As indicated above, the nucleic acid sequence may be substantially a depicted in any one of SEQ ID NO: 1 to SEQ ID NO: 36 or fragments thereof or sequences having at least 90% identity to the above sequence as explained above. Alternatively, due to the degenerative nature of the genetic code, the sequence may be a sequence coding for any one of the amino acid sequence of SEQ ID NO: 37 to SEQ ID NO: 72, or fragments or analogs of said amino acid sequence.

A. Preparation of nucleic acid sequences

The nucleic acid sequences may be obtained by screening cDNA libraries using oligonucleotide probes which can hybridize to or PCR-amplify nucleic acid sequences which encode the variant products disclosed above. cDNA libraries prepared from a variety of tissues are commercially available and procedures for screening and isolating cDNA clones are well-known to those of skill in the art. Such techniques are described in, for example, Sambrook *et al.* (1989) Molecular Cloning: A Laboratory Manual (2nd Edition), Cold Spring Harbor Press, Plainview, N.Y. and Ausubel FM et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y.

The nucleic acid sequences may be extended to obtain upstream and downstream sequences such as promoters, regulatory elements, and 5' and 3'

untranslated regions (UTRs). Extension of the available transcript sequence may be performed by numerous methods known to those of skill in the art, such as PCR or primer extension (Sambrook *et al., supra*), or by the RACE method using, for example, the Marathon RACE kit (Clontech, Cat. # K1802-1).

Alternatively, the technique of *"restriction-site"* PCR (Gobinda *et al. PCR Methods Applic.* **2**:318-22, (1993)), which uses universal primers to retrieve flanking sequence adjacent a known locus, may be employed. First, genomic DNA is amplified in the presence of primer to a linker sequence and a primer specific to the known region. The amplified sequences are subjected to a second round of PCR with the same linker primer and another specific primer internal to the first one. Products of each round of PCR are transcribed with an appropriate RNA polymerase and sequenced using reverse transcriptase.

Inverse PCR can be used to amplify or extend sequences using divergent primers based on a known region (Triglia, T. *et al., Nucleic Acids Res.* **16**:8186, (1988)). The primers may be designed using OLIGO(R) 4.06 Primer Analysis Software (1992; National Biosciences Inc, Plymouth, Minn.), or another appropriate program, to be 22-30 nucleotides in length, to have a GC content of 50% or more, and to anneal to the target sequence at temperatures about 68-72°C. The method uses several restriction enzymes to generate a suitable fragment in the known region of a gene. The fragment is then circularized by intramolecular ligation and used as a PCR template.

Capture PCR (Lagerstrom, M. *et al., PCR Methods Applic.* **1**:111-19, (1991)) is a method for PCR amplification of DNA fragments adjacent to a known sequence in human and yeast artificial chromosome DNA. Capture PCR also requires multiple restriction enzyme digestions and ligations to place an engineered double-stranded sequence into a flanking part of the DNA molecule before PCR.

Another method which may be used to retrieve flanking sequences is that of Parker, J.D., *et al., Nucleic Acids Res.,* **19**:3055-60, (1991)). Additionally, one can use PCR, nested primers and PromoterFinder™ libraries to *"walk in"* genomic

DNA (PromoterFinder™; Clontech, Palo Alto, CA). This process avoids the need to screen libraries and is useful in finding intron/exon junctions. Preferred libraries for screening for full length cDNAs are ones that have been size-selected to include larger cDNAs. Also, random primed libraries are preferred in that they will contain more sequences which contain the 5' and upstream regions of genes.

A randomly primed library may be particularly useful if an oligo d(T) library does not yield a full-length cDNA. Genomic libraries are useful for extension into the 5' nontranslated regulatory region.

The nucleic acid sequences and oligonucleotides of the invention can also be prepared by solid-phase methods, according to known synthetic methods. Typically, fragments of up to about 100 bases are individually synthesized, then joined to form continuous sequences up to several hundred bases.

B. Use of variant nucleic acid sequence for the production of variant products

In accordance with the present invention, nucleic acid sequences specified above may be used as recombinant DNA molecules that direct the expression of variant products.

As will be understood by those of skill in the art, it may be advantageous to produce variant product-encoding nucleotide sequences possessing codons other than those which appear in any one of SEQ ID NO: 1 to SEQ ID NO: 36 which are those which naturally occur in the human genome. Codons preferred by a particular prokaryotic or eukaryotic host (Murray, E. *et al. Nuc Acids Res.*, 17:477-508, (1989)) can be selected, for example, to increase the rate of variant product expression or to produce recombinant RNA transcripts having desirable properties, such as a longer half-life, than transcripts produced from naturally occurring sequence.

The nucleic acid sequences of the present invention can be engineered in order to alter a variant product coding sequence for a variety of reasons, including but not limited to, alterations which modify the cloning, processing

and/or expression of the product. For example, alterations may be introduced using techniques which are well known in the art, e.g., site-directed mutagenesis, to insert new restriction sites, to alter glycosylation patterns, to change codon preference, etc.

The present invention also includes recombinant constructs comprising one or more of the sequences as broadly described above. The constructs comprise a vector, such as a plasmid or viral vector, into which a nucleic acid sequence of the invention has been inserted, in a forward or reverse orientation. In a preferred aspect of this embodiment, the construct further comprises regulatory sequences, including, for example, a promoter, operably linked to the sequence. Large numbers of suitable vectors and promoters are known to those of skill in the art, and are commercially available. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are also described in Sambrook, *et al., (supra).*

The present invention also relates to host cells which are genetically engineered with vectors of the invention, and the production of the product of the invention by recombinant techniques. Host cells are genetically engineered (i.e., transduced, transformed or transfected) with the vectors of this invention which may be, for example, a cloning vector or an expression vector. The vector may be, for example, in the form of a plasmid, a viral particle, a phage, etc. The engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the expression of the variant nucleic acid sequence. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to those skilled in the art.

The nucleic acid sequences of the present invention may be included in any one of a variety of expression vectors for expressing a product. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences, e.g., derivatives of SV40; bacterial plasmids; phage DNA; baculovirus; yeast plasmids; vectors derived from combinations of plasmids and phage DNA, viral

DNA such as vaccinia, adenovirus, fowl pox virus, and pseudorabies. However, any other vector may be used as long as it is replicable and viable in the host. The appropriate DNA sequence may be inserted into the vector by a variety of procedures. In general, the DNA sequence is inserted into an appropriate restriction endonuclease site(s) by procedures known in the art. Such procedures and related sub-cloning procedures are deemed to be within the scope of those skilled in the art.

The DNA sequence in the expression vector is operatively linked to an appropriate transcription control sequence (promoter) to direct mRNA synthesis. Examples of such promoters include: LTR or SV40 promoter, the *E.coli lac* or *trp* promoter, the phage lambda *PL* promoter, and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses. The expression vector also contains a ribosome binding site for translation initiation, and a transcription terminator. The vector may also include appropriate sequences for amplifying expression. In addition, the expression vectors preferably contain one or more selectable marker genes to provide a phenotypic trait for selection of transformed host cells such as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or ampicillin resistance in *E.coli.*

The vector containing the appropriate DNA sequence as described above, as well as an appropriate promoter or control sequence, may be employed to transform an appropriate host to permit the host to express the protein. Examples of appropriate expression hosts include: bacterial cells, such as *E.coli*, *Streptomyces, Salmonella typhimurium*; fungal cells, such as yeast; insect cells such as *Drosophila* and *Spodoptera* Sf9; animal cells such as CHO, COS, HEK 293 or Bowes melanoma; adenoviruses; plant cells, etc. The selection of an appropriate host is deemed to be within the scope of those skilled in the art from the teachings herein. The invention is not limited by the host cells employed.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the variant product. For example, when

large quantities of variant product are needed for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be desirable. Such vectors include, but are not limited to, multifunctional *E.coli* cloning and expression vectors such as *Bluescript*(R) (Stratagene), in which the variant polypeptide coding sequence may be ligated into the vector in-frame with sequences for the amino-terminal Met and the subsequent 7 residues of beta-galactosidase so that a hybrid protein is produced; *pIN* vectors (Van Heeke & Schuster *J. Biol. Chem.* **264**:5503-5509, (1989)); *pET* vectors (Novagen, Madison WI); and the like.

In the yeast *Saccharomyces cerevisiae* a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase and PGH may be used. For reviews, see Ausubel *et al. (supra)* and Grant *et al.*, (*Methods in Enzymology* **153**:516-544, (1987)).

In cases where plant expression vectors are used, the expression of a sequence encoding variant product may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of *CaMV* (Brisson *et al., Nature* **310**:511-514. (1984)) may be used alone or in combination with the omega leader sequence from TMV (Takamatsu *et al.*, *EMBO J.*, **6**:307-311, (1987)). Alternatively, plant promoters such as the small subunit of RUBISCO (Coruzzi *et al., EMBO J.* **3**:1671-1680, (1984); Broglie *et al., Science* **224**:838-843, (1984)); or heat shock promoters (Winter J and Sinibaldi R.M., *Results Probl. Cell Differ.,* **17**:85-105, (1991)) may be used. These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. For reviews of such techniques, see Hobbs S. or Murry L.E. (1992) in McGraw Hill Yearbook of Science and Technology, McGraw Hill, New York, N.Y., pp 191-196; or Weissbach and Weissbach (1988) *Methods for Plant Molecular Biology*, Academic Press, New York, N.Y., pp 421-463.

Variant product may also be expressed in an insect system. In one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a

vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The variant product coding sequence may be cloned into a nonessential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of variant coding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein coat. The recombinant viruses are then used to infect *S. frugiperda* cells or *Trichoplusia* larvae in which variant protein is expressed (Smith *et al., J. Virol.* 46:584, (1983); Engelhard, E.K. *et al., Proc. Nat. Acad. Sci.* **91**:3224-7, (1994)).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, a variant product coding sequence may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a nonessential E1 or E3 region of the viral genome will result in a viable virus capable of expressing variant protein in infected host cells (Logan and Shenk, *Proc. Natl. Acad. Sci.* **81**:3655-59, (1984). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be required for efficient translation of a variant product coding sequence. These signals include the ATG initiation codon and adjacent sequences. In cases where variant product coding sequence, its initiation codon and upstream sequences are inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous transcriptional control signals including the ATG initiation codon must be provided. Furthermore, the initiation codon must be in the correct reading frame to ensure transcription of the entire insert. Exogenous transcriptional elements and initiation codons can be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate to the cell system in use (Scharf, D. *et al.,*

(1994) *Results Probl. Cell Differ.*, **20**:125-62, (1994); Bittner et al., *Methods in Enzymol* **153**:516-544, (1987)).

In a further embodiment, the present invention relates to host cells containing the above-described constructs. The host cell can be a higher eukaryotic cell, such as a mammalian cell, or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-Dextran mediated transfection, or electroporation (Davis, L., Dibner, M., and Battey, I. (1986) Basic Methods in Molecular Biology). Cell-free translation systems can also be employed to produce polypeptides using RNAs derived from the DNA constructs of the present invention.

A host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the protein include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation. Post-translational processing which cleaves a *"pre-pro"* form of the protein may also be important for correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, 293, WI38, etc. have specific cellular machinery and characteristic mechanisms for such post-translational activities and may be chosen to ensure the correct modification and processing of the introduced, foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express variant product may be transformed using expression vectors which contain viral origins of replication or endogenous expression elements and a selectable marker gene. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the

introduced sequences. Resistant clumps of stably transformed cells can be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler M., *et al.*, *Cell* **11**:223-32, (1977)) and adenine phosphoribosyltransferase (Lowy I., *et al.*, *Cell* **22**:817-23, (1980)) genes which can be employed in *tk-* or *aprt-* cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, *dhfr* which confers resistance to methotrexate (Wigler M., *et al., Proc. Natl. Acad. Sci.* 77:3567-70, (1980)); *npt*, which confers resistance to the aminoglycosides neomycin and G-418 (Colbere-Garapin, F. *et al., J. Mol. Biol.*, **150**:1-14, (1981)) and *als* or *pat*, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, *trpB*, which allows cells to utilize indole in place of tryptophan, or *hisD*, which allows cells to utilize histinol in place of histidine (Hartman S.C. and R.C. Mulligan, *Proc. Natl. Acad. Sci.* **85**:8047-51, (1988)). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate, GUS, and luciferase and its substrates, luciferin and ATP, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C.A. *et. al., Methods Mol. Biol.,* 55:121-131, (1995)).

Host cells transformed with a nucleotide sequence encoding variant product may be cultured under conditions suitable for the expression and recovery of the encoded protein from cell culture. The product produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing nucleic acid sequences encoding variant product can be designed with signal sequences which direct secretion of variant product through a prokaryotic or eukaryotic cell membrane.

The variant product may also be expressed as a recombinant protein with one or more additional polypeptide domains added to facilitate protein purification. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp, Seattle, Wash.). The inclusion of a protease-cleavable polypeptide linker sequence between the purification domain and variant product is useful to facilitate purification. One such expression vector provides for expression of a fusion protein compromising a variant polypeptide fused to a polyhistidine region separated by an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography, as described in Porath, *et al.*, *Protein Expression and Purification,* **3**:263-281, (1992)) while the enterokinase cleavage site provides a means for isolating variant polypeptide from the fusion protein. *pGEX* vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to ligand-agarose beads (e.g., glutathione-agarose in the case of GST-fusions) followed by elution in the presence of free ligand.

Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced by appropriate means (e.g., temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents, or other methods, which are well know to those skilled in the art.

The variant products can be recovered and purified from recombinant cell cultures by any of a number of methods well known in the art, including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, and lectin chromatography. Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps.

C. Diagnostic applications utilizing nucleic acid sequences

The nucleic acid sequences of the present invention may be used for a variety of diagnostic purposes. The nucleic acid sequences may be used to detect and quantitate expression of the variant in patient's cells, e.g. biopsied tissues, by detecting the presence of mRNA coding for variant product. Alternatively, the assay may be used to detect soluble variant in the serum or blood. This assay typically involves obtaining total mRNA from the tissue or serum and contacting the mRNA with a nucleic acid probe. The probe is a nucleic acid molecule of at least 20 nucleotides, preferably 20-30 nucleotides, capable of specifically hybridizing with a sequence included within the sequence of a nucleic acid molecule encoding variant product under hybridizing conditions, detecting the presence of mRNA hybridized to the probe, and thereby detecting the expression of variant. This assay can be used to distinguish between absence, presence, and excess expression of variant product and to monitor levels of variant expression during therapeutic intervention. In addition, the assay may be used to compare the levels of the variant of the invention to the levels of the original sequence from which it has been varied or to levels of other variants, which comparison may have some physiological meaning.

The invention also contemplates the use of the nucleic acid sequences as a diagnostic for diseases resulting from inherited defective variant sequences, or

diseases in which the ratio of the amount of the original sequence from which the variant was varied to the novel variants of the invention is altered. These sequences can be detected by comparing the sequences of the defective (i.e., mutant) variant coding region with that of a normal coding region. Association of the sequence coding for mutant variant product with abnormal variant product activity may be verified. In addition, sequences encoding mutant variant products can be inserted into a suitable vector for expression in a functional assay system (e.g., colorimetric assay, complementation experiments in a variant protein deficient strain of HEK293 cells) as yet another means to verify or identify mutations. Once mutant genes have been identified, one can then screen populations of interest for carriers of the mutant gene.

Individuals carrying mutations in the nucleic acid sequence of the present invention may be detected at the DNA level by a variety of techniques. Nucleic acids used for diagnosis may be obtained from a patient's cells, including but not limited to such as from blood, urine, saliva, placenta, tissue biopsy and autopsy material. Genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR (Saiki, *et al.*, *Nature* **324**:163-166, (1986)) prior to analysis. RNA or cDNA may also be used for the same purpose. As an example, PCR primers complementary to the nucleic acid of the present invention can be used to identify and analyze mutations in the gene of the present invention. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype.

Point mutations can be identified by hybridizing amplified DNA to radiolabeled RNA of the invention or alternatively, radiolabeled antisense DNA sequences of the invention. Sequence changes at specific locations may also be revealed by nuclease protection assays, such RNase and S1 protection or the chemical cleavage method (e.g. Cotton, *et alProc. Natl. Acad. Sci.* USA, **85**:4397-4401, (1985)), or by differences in melting temperatures. *"Molecular beacons"* (Kostrikis L.G. *et al.*, Science **279**:1228-1229, (1998)), hairpin-shaped, single-stranded synthetic oligonucleotides containing probe sequences which are

complementary to the nucleic acid of the present invention, may also be used to detect point mutations or other sequence changes as well as monitor expression levels of variant product. Such diagnostics would be particularly useful for prenatal testing.

Another method for detecting mutations uses two DNA probes which are designed to hybridize to adjacent regions of a target, with abutting bases, where the region of known or suspected mutation(s) is at or near the abutting bases. The two probes may be joined at the abutting bases, e.g., in the presence of a ligase enzyme, but only if both probes are correctly base paired in the region of probe junction. The presence or absence of mutations is then detectable by the presence or absence of ligated probe.

Also suitable for detecting mutations in the variant product coding sequence are oligonucleotide array methods based on sequencing by hybridization (SBH), as described, for example, in U.S. Patent No. 5,547,839. In a typical method, the DNA target analyte is hybridized with an array of oligonucleotides formed on a microchip. The sequence of the target can then be "read" from the pattern of target binding to the array.

D. Gene mapping utilizing nucleic acid sequences

The nucleic acid sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Moreover, there is a current need for identifying particular sites on the chromosome. Few chromosome marking reagents based on actual sequence data (repeat polymorphisms) are presently available for marking chromosomal location. The mapping of DNAs to chromosomes according to the present invention is an important first step in correlating those sequences with genes associated with disease.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 20-30 bp) from the variant cDNA. Computer analysis of the

3' untranslated region is used to rapidly select primers that do not span more than one exon in the genomic DNA, which would complicate the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the primer will yield an amplified fragment.

PCR mapping of somatic cell hybrids or using instead radiation hybrids are rapid procedures for assigning a particular DNA to a particular chromosome. Using the present invention with the same oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes or pools of large genomic clones in an analogous manner. Other mapping strategies that can similarly be used to map to its chromosome include *in situ* hybridization, prescreening with labeled flow-sorted chromosomes and preselection by hybridization to construct chromosome specific-cDNA libraries.

Fluorescence *in situ* hybridization (FISH) of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can be used with cDNA as short as 50 or 60 bases. For a review of this technique, see Verma *et al., Human Chromosomes: a Manual of Basic Techniques*, (1988) Pergamon Press, New York.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, for example, in the OMIM database (Center for Medical Genetics, Johns Hopkins University, Baltimore, MD and National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD). The OMIM gene map presents the cytogenetic map location of disease genes and other expressed genes. The OMIM database provides information on diseases associated with the chromosomal location. Such associations include the results of linkage analysis mapped to this interval, and the correlation of translocations and other chromosomal aberrations in this area with the advent of polygenic diseases, such as cancer, in general and prostate cancer in particular.

E. Therapeutic applications of nucleic acid sequences

Nucleic acid sequences of the invention may also be used for therapeutic purposes. Turning first to the second aspect of the invention (i.e. inhibition of expression of variant), expression of variant product may be modulated through antisense technology, which controls gene expression through hybridization of complementary nucleic acid sequences, i.e. antisense DNA or RNA, to the control, 5' or regulatory regions of the gene encoding variant product. For example, the 5' coding portion of the nucleic acid sequence sequence which codes for the product of the present invention is used to design an antisense oligonucleotide of from about 10 to 40 base pairs in length. Oligonucleotides derived from the transcription start site, e.g. between positions -10 and +10 from the start site, are preferred. An antisense DNA oligonucleotide is designed to be complementary to a region of the nucleic acid sequence involved in transcription (Lee *et al., Nucl. Acids, Res.*, **6**:3073, (1979); Cooney et al., Science **241**:456, (1988); and Dervan *et al., Science* **251**:1360, (1991)), thereby preventing transcription and the production of the variant products. An antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into the variant products (Okano *J. Neurochem.* **56**:560, (1991)). The antisense constructs can be delivered to cells by procedures known in the art such that the antisense RNA or DNA may be expressed *in vivo*. The antisense may be antisense mRNA or DNA sequence capable of coding such antisense mRNA. The antisense mRNA or the DNA coding thereof can be complementary to the full sequence of nucleic acid sequences coding for the variant protein or to a fragment of such a sequence which is sufficient to inhibit production of a protein product.

Turning now to the first aspect of the invention, i.e. expression of variant, expression of variant product may be increased by providing coding sequences for coding for said product under the control of suitable control elements ending its expression in the desired host.

The nucleic acid sequences of the invention may be employed in combination with a suitable pharmaceutical carrier. Such compositions comprise a therapeutically effective amount of the compound, and a pharmaceutically acceptable carrier or excipient. Such a carrier includes but is not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The formulation should suit the mode of administration.

The products of the invention as well as any activators and deactivators compounds (see below) which are polypeptides, may also be employed in accordance with the present invention by expression of such polypeptides *in vivo*, which is often referred to as *"gene therapy."* Cells from a patient may be engineered with a nucleic acid sequence (DNA or RNA) encoding a polypeptide *ex vivo*, with the engineered cells then being provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, cells may be engineered by procedures known in the art by use of a retroviral particle containing RNA encoding a polypeptide of the present invention.

Similarly, cells may be engineered in vivo for expression of a polypeptide *in vivo* by procedures known in the art. As known in the art, a producer cell for producing a retroviral particle containing RNA encoding the polypeptide of the present invention may be administered to a patient for engineering cells *in vivo* and expression of the polypeptide *in vivo*. These and other methods for administering a product of the present invention by such method should be apparent to those skilled in the art from the teachings of the present invention. For example, the expression vehicle for engineering cells may be other than a retrovirus, for example, an adenovirus which may be used to engineer cells *in vivo* after combination with a suitable delivery vehicle.

Retroviruses from which the retroviral plasmid vectors mentioned above may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, retroviruses such as Rous Sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, adenovirus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the *PE501*, *PA317*, *psi-2*, *psi-AM*, *PA12*, *T19-14X*, *VT-19-17-H2*, *psi-CRE*, *psi-CRIP*, *GP+E-86*, *GP+envAm12*, and *DAN* cell lines as described in Miller (*Human Gene Therapy*, Vol. **1**, pg. 5-14, (1990)). The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and $CaPO_4$ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

The producer cell line generates infectious retroviral vector particles which include the nucleic acid sequence(s) encoding the polypeptides. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express the nucleic acid sequence(s) encoding the polypeptide. Eukaryotic cells which may be transduced include, but are not limited to, embryonic stem cells, embryonic carcinoma cells, as well as hematopoietic stem cells, hepatocytes, fibroblasts, myoblasts, keratinocytes, endothelial cells, and bronchial epithelial cells.

The genes introduced into cells may be placed under the control of inducible promoters, such as the radiation-inducible Egr-1 promoter, (Maceri, H.J., *et al., Cancer Res.*, **56**(19):4311 (1996)), to stimulate variant production or antisense inhibition in response to radiation, eg., radiation therapy for treating tumors.

Example III. Variant product

The substantially purified variant product of the invention has been defined above as the product coded from the nucleic acid sequence of the invention. Preferably the amino acid sequence is an amino acid sequence having at least 90% identity to any one of the sequences identified as SEQ ID NO: 37 to SEQ ID NO: 72 provided that the amino acid sequence is not identical to that of

the original sequence from which it has been varied. The protein or polypeptide may be in mature and/or modified form, also as defined above. Also contemplated are protein fragments having at least 10 contiguous amino acid residues, preferably at least 10-20 residues, derived from the variant product, as well as homologues as explained above.

The sequence variations are preferably those that are considered conserved substitutions, as defined above. Thus, for example, a protein with a sequence having at least 90% sequence identity with any of the products identified as SEQ ID NO: 37 to SEQ ID NO: 72, preferably by utilizing conserved substitutions as defined above is also part of the invention, and provided that it is not identical to the original peptide from which it has been varied. In a more specific embodiment, the protein has or contains any one of the sequence identified as SEQ ID NO: 37 to SEQ ID NO: 72. The variant product may be (i) one in which one or more of the amino acid residues in a sequence listed above are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue), or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the variant product is fused with another compound, such as a compound to increase the half-life of the protein (for example, polyethylene glycol (PEG)), or a moiety which serves as targeting means to direct the protein to its target tissue or target cell population (such as an antibody), or (iv) one in which additional amino acids are fused to the variant product. Such fragments, variants and derivatives are deemed to be within the scope of those skilled in the art from the teachings herein.

A. Preparation of variant product

Recombinant methods for producing and isolating the variant product, and fragments of the protein are described above.

In addition to recombinant production, fragments and portions of variant product may be produced by direct peptide synthesis using solid-phase techniques (cf. Stewart *et al.*, (1969) Solid-Phase Peptide Synthesis, WH Freeman Co, San

Francisco; Merrifield J., *J. Am. Chem. Soc.,* **85**:2149-2154, (1963)). In vitro peptide synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer, Foster City, Calif.) in accordance with the instructions provided by the manufacturer. Fragments of variant product may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

II. Therapeutic uses and compositions utilizing the variant product

The variant product of the invention is generally useful in treating diseases and disorders which are characterized by a lower than normal level of variant expression, and or diseases which can be cured or ameliorated by raising the level of the variant product, even if the level is normal.

Variant products or fragments may be administered by any of a number of routes and methods designed to provide a consistent and predictable concentration of compound at the target organ or tissue. The product-containing compositions may be administered alone or in combination with other agents, such as stabilizing compounds, and/or in combination with other pharmaceutical agents such as drugs or hormones.

Variant product-containing compositions may be administered by a number of routes including, but not limited to oral, intravenous, intramuscular, transdermal, subcutaneous, topical, sublingual, or rectal means as well as by nasal application. Variant product-containing compositions may also be administered via liposomes. Such administration routes and appropriate formulations are generally known to those of skill in the art.

The product can be given via intravenous or intraperitoneal injection. Similarly, the product may be injected to other localized regions of the body. The product may also be administered via nasal insufflation. Enteral administration is also possible. For such administration, the product should be formulated into an

appropriate capsule or elixir for oral administration, or into a suppository for rectal administration.

The foregoing exemplary administration modes will likely require that the product be formulated into an appropriate carrier, including ointments, gels, suppositories. Appropriate formulations are well known to persons skilled in the art.

Dosage of the product will vary, depending upon the potency and therapeutic index of the particular polypeptide selected.

A therapeutic composition for use in the treatment method can include the product in a sterile injectable solution, the polypeptide in an oral delivery vehicle, the product in an aerosol suitable for nasal administration, or the product in a nebulized form, all prepared according to well known methods. Such compositions comprise a therapeutically effective amount of the compound, and a pharmaceutically acceptable carrier or excipient. Such a carrier includes but is not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The product of the invention may also be used to modulate endothelial differentiation and proliferation as well as to modulate apoptosis either *ex vivo* or *in vitro*, for example, in cell cultures.

Example IV. Screening methods for activators and deactivators (inhibitors)

The present invention also includes an assay for identifying molecules, such as synthetic drugs, antibodies, peptides, or other molecules, which have a modulating effect on the activity of the variant product, e.g. activators or deactivators of the variant product of the present invention. Such an assay comprises the steps of providing an variant product encoded by the nucleic acid sequences of the present invention, contacting the variant protein with one or more candidate molecules to determine the candidate molecules modulating effect on the activity of the variant product, and selecting from the molecules a candidate's molecule capable of modulating variant product physiological activity.

The variant product, its catalytic or immunogenic fragments or oligopeptides thereof, can be used for screening therapeutic compounds in any of a variety of drug screening techniques. The fragment employed in such a test may be free in solution, affixed to a solid support, borne on a cell membrane or located intracellularly. The formation of binding complexes, between variant product and the agent being tested, may be measured. Alternatively, the activator or deactivator may work by serving as agonist or antagonist, respectively, of the variant receptor, binding entity or target site, and their effect may be determined in connection with any of the above.

Another technique for drug screening which may be used provides for high throughput screening of compounds having suitable binding affinity to the variant product is described in detail by Geysen in PCT Application WO 84/03564, published on Sep. 13, 1984. In summary, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with the full variant product or with fragments of variant product and washed. Bound variant product is then detected by methods well known in the art. Substantially purified variant product can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

Antibodies to the variant product, as described in Example VI below, may also be used in screening assays according to methods well known in the art. For example, a *"sandwich"* assay may be performed, in which an anti-variant antibody is affixed to a solid surface such as a microtiter plate and variant product is added. Such an assay can be used to capture compounds which bind to the variant product. Alternatively, such an assay may be used to measure the ability of compounds to influence with the binding of variant product to the variant receptor, and then select those compounds which effect the binding.

Example V. Anti-variant antibodies

A. Synthesis

In still another aspect of the invention, the purified variant product is used to produce anti-variant antibodies which have diagnostic and therapeutic uses related to the activity, distribution, and expression of the variant product.

Antibodies to the variant product may be generated by methods well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, humanized, single chain, Fab fragments and fragments produced by an Fab expression library. Antibodies, i.e., those which inhibit dimer formation, are especially preferred for therapeutic use.

A fragment of the variant product for antibody induction does not require biological activity but have to feature immunological activity; however, the protein fragment or oligopeptide must be antigenic. Peptides used to induce specific antibodies may have an amino acid sequence consisting of at least five amino acids, preferably at least 10 amino acids of the sequences specified in any one of SEQ ID NO: 37 to SEQ ID NO: 72. Preferably they should mimic a portion of the amino acid sequence of the natural protein and may contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of variant protein amino acids may be fused with those of another protein such as keyhole limpet hemocyanin and antibody produced against the chimeric molecule. Procedures well known in the art can be used for the production of antibodies to variant product.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, etc may be immunized by injection with variant product or any portion, fragment or oligopeptide which retains immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include but are not limited to Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet

hemocyanin, and dinitrophenol. BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are potentially useful human adjuvants.

Monoclonal antibodies to variant protein may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include but are not limited to the hybridoma technique originally described by Koehler and Milstein (*Nature* **256**:495-497, (1975)), the human B-cell hybridoma technique (Kosbor *et al., Immunol. Today* **4**:72, (1983); Cote *et al., Proc. Natl. Acad. Sci.* **80**:2026-2030, (1983)) and the EBV-hybridoma technique (Cole, *et al., Mol. Cell Biol.* 62:109-120, (1984)).

Techniques developed for the production of *"chimeric antibodies"*, the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity can also be used (Morrison *et al., Proc. Natl. Acad. Sci.* **81**:6851-6855, (1984); Neuberger *et al., Nature* **312**:604-608, (1984); Takeda *et al., Nature* **314**:452-454, (1985)). Alternatively, techniques described for the production of single chain antibodies (U.S. Pat. No. 4,946,778) can be adapted to produce single-chain antibodies specific for the variant protein.

Antibodies may also be produced by inducing *in vivo* production in the lymphocyte population or by screening recombinant immunoglobulin libraries or panels of highly specific binding reagents as disclosed in Orlandi *et al.* (*Proc. Natl. Acad. Sci.* **86**:3833-3837, 1989)), and Winter G and Milstein C., (*Nature* **349**:293-299, (1991)).

Antibody fragments which contain specific binding sites for variant protein may also be generated. For example, such fragments include, but are not limited to, the $F(ab')_2$ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity (Huse W.D. *et al., Science* 256:1275-1281, (1989)).

B. Diagnostic applications of antibodies

A variety of protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the formation of complexes between the variant product and its specific antibody and the measurement of complex formation. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two noninterfering epitopes on a specific variant product is preferred, but a competitive binding assay may also be employed. These assays are described in Maddox D.E., *et al.*, (*J. Exp. Med.* **158**:1211, (1983)).

Antibodies which specifically bind variant product are useful for the diagnosis of conditions or diseases characterized by expression of the novel variant of the invention (where normally it is not expressed) by over or under expression of variant as well as for detection of diseases in which the proportion between the amount of the variants of the invention and the original sequence from which it varied is altered. Alternatively, such antibodies may be used in assays to monitor patients being treated with variant product, its activators, or its deactivators. Diagnostic assays for variant protein include methods utilizing the antibody and a label to detect variant product in human body fluids or extracts of cells or tissues. The products and antibodies of the present invention may be used with or without modification. Frequently, the proteins and antibodies will be labeled by joining them, either covalently or noncovalently, with a reporter molecule. A wide variety of reporter molecules are known in the art.

A variety of protocols for measuring the variant product, using either polyclonal or monoclonal antibodies specific for the respective protein are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescent activated cell sorting (FACS). As noted above, a two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on variant product is

preferred, but a competitive binding assay may be employed. These assays are described, among other places, in Maddox, *et al. (supra)*. Such protocols provide a basis for diagnosing altered or abnormal levels of variant product expression. Normal or standard values for variant product expression are established by combining body fluids or cell extracts taken from normal subjects, preferably human, with antibody to variant product under conditions suitable for complex formation which are well known in the art. The amount of standard complex formation may be quantified by various methods, preferably by photometric methods. Then, standard values obtained from normal samples may be compared with values obtained from samples from subjects potentially affected by disease. Deviation between standard and subject values establishes the presence of disease state.

The antibody assays are useful to determine the level of variant product present in a body fluid sample, in order to determine whether it is being expressed at all, whether it is being overexpressed or underexpressed in the tissue, or as an indication of how variant levels of variable products are responding to drug treatment.

By another aspect the invention concerns methods for determining the presence or level of various anti-variant antibodies in a biological sample obtained from patients, such as blood or serum sample using as an antigen the variant product. Determination of said antibodies may be indicative to a plurality of pathological conditions or diseases.

C. Therapeutic uses of antibodies

In addition to their diagnostic use the antibodies may have a therapeutical utility in blocking or decreasing the activity of the variant product in pathological conditions where beneficial effect can be achieved by such a decrease.

The antibody employed is preferably a humanized monoclonal antibody, or a human Mab produced by known globulin-gene library methods. The antibody is administered typically as a sterile solution by IV injection, although

other parenteral routes may be suitable. Typically, the antibody is administered in an amount between about 1-15 mg/kg body weight of the subject. Treatment is continued, e.g., with dosing every 1-7 days, until a therapeutic improvement is seen.

Although the invention has been described with reference to specific methods and embodiments, it is appreciated that various modifications and changes may be made without departing from the invention.

CLAIMS:

1. An isolated nucleic acid sequence, of an alternative splicing variant, selected from the group consisting of:

(i) the nucleic acid sequence depicted in any one of SEQ ID NO: 1 to SEQ ID NO: 36;

(ii) nucleic acid sequences having at least 90% identity with the sequence of (i) with the proviso that each sequence is different than the original nucleic acid sequence from which the sequences of (i) have been varied by alternative splicing; and

(iii) fragments of (i) or (ii) of at least 20 b.p., provided that said fragment contains a sequence which is not present, as a continuous stretch of nucleotides, in the original nucleic acid sequence from which the sequences of (i) have been varied by alternative splicing.

2. An isolated nucleic acid sequence complementary to the nucleic acid sequence of Claim 1.

3. An amino acid sequence selected from the group consisting of:

(i) an amino acid sequence coded by the isolated nucleic acid sequence of alternative splice variants of Claim 1;

(ב) homologues of the amino acid sequences of (i) in which one or more amino acids has been added, deleted, replaced or chemically modified in the region or adjacent to the region where the amino acid sequences differs from the original amino acid sequence, coded by the original nucleic acid sequence from which the variant has been varied.

4. An amino acid sequence according to Claim 3, as depicted in any one of SEQ ID NO: 37 to SEQ ID NO: 72.

5. An isolated nucleic acid sequence coding for any one of the amino acid sequences of Claim 3 or 4.

6. A purified antibody which binds specifically to any of the amino acid sequence of Claim 3 or 4.

7. An expression vector comprising any one of the nucleic acid sequences of Claim 1 or 5 and control elements for the expression of the nucleic acid sequence in a suitable host.

8. An expression vector comprising any one of the nucleic acid sequences of Claim 2, and control elements for the expression of the nucleic acid sequences in a suitable host.

9. A host cell transfected by the expression vector of Claim 7 or 8.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active ingredient an agent selected from the group consisting of:

(i) the expression vector of Claim 7; and

(ii) any one of the amino acid sequences of Claim 3 or 4.

11. A pharmaceutical composition according to Claim 10, for treatment of diseases which can be ameliorated or cured by raising the level of any one of the amino acid sequences depicted in SEQ ID NO: 37 to SEQ ID NO: 72.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active ingredient an agent selected from the group consisting of:

(i) any one of the nucleic acid sequences of Claim 2;

(ii) the expression vector of Claim 8; and

(iii) the purified antibody of Claim 6.

13. A pharmaceutical composition according to Claim 12, for treatment of diseases which can be ameliorated or cured by decreasing the level of any one of the amino acid sequences depicted in SEQ ID NO: 37 to SEQ ID NO: 72.

14. A method for detecting an variant nucleic acid sequence in a biological sample, comprising the steps of:

(a) hybridizing to nucleic acid material of said biological sample any one of the nucleic acid sequences of Claim 1 or 2; and

(b) detecting said hybridization complex;

wherein the presence of said hybridization complex correlates with the presence of an variant nucleic acid sequence in the said biological sample.

15. A method for determining the level of variant nucleic acid sequences in a biological sample comprising the steps of:

(a) hybridizing to nucleic acid material of said biological sample any one of the nucleic acid sequences of Claim 1 or 2; and

(b) determining the amount of hybridization complexes and normalizing said amount to provide the level of the variant nucleic acid sequences in the sample.

16. A method for determining the ratio between the level of variant of the nucleic acid sequence in a first biological sample and the level of the original sequence from which the variant has been varied by alternative splicing in a second biological sample comprising:

(i) determining the level of the variant nucleic acid sequence in the first biological sample according to the method of Claim 15;

(ii) determining the level of the original sequence in the second biological sample; and

(iii) comprising the levels obtained in (a) and (b) to give said ratio.

17. A method according to Claim 16, wherein said first and said second biological samples are the same sample.

18. A method according to any of Claims 14 to 17, wherein the nucleic acid material of said biological sample are mRNA transcripts.

19. A method according to Claim 18, where the nucleic acid sequence is present in a nucleic acid chip.

20. A method for identifying candidate compounds capable of binding to the variant product and modulating its activity the method comprising:

(i) providing any one of the amino acid sequences as defined in Claim 3 or 4;

(ii) contacting a candidate compound with said amino acid sequence;

(iii) determining the effect of said candidate compound on the biological activity of said protein or polypeptide and selecting those compounds which show a significant effect on said biological activity.

21. A method according to Claim 20, wherein the compound is an activator and the measured effect is increase in the biological activity.

22. A method according to Claim 20, wherein the compound is an deactivator and the effect is decrease in the biological activity.

23. An activator of any one of the amino acid sequences of Claim 3 or 4.

24. An deactivator of any one of the amino acid sequences of Claims 3 or 4.

25. A method for detecting any one of the amino acid sequences of Claim 3 or 4 in a biological sample, comprising the steps of:

(a) contacting with said biological sample the antibody of Claim 8, thereby forming an antibody-antigen complex; and

(b) detecting said antibody-antigen complex

wherein the presence of said antibody-antigen complex correlates with the presence of the desired amino acid in said biological sample.

26. A method for detecting the level of the amino acid sequence of any one of Claim 3 or 4 in a biological sample, comprising the steps of:

(a) contacting with said biological sample the antibody of Claim 8, thereby forming an antibody-antigen complex; and

(b) detecting the amount of said antibody-antigen complex and normalizing said amount to provide the level of said amino acid sequence in the sample.

27. A method for determining the ratio between the level of any one of the amino acid sequences of Claims 3 or 4 present in a first biological sample and the level of the original amino acid sequences from which they were varied by alternative splicing, present in a second biological sample, the method comprising:

(i) determining the level of the amino acid sequences of Claims 3 or 4 into a first sample by the method of Claim 26;

(ii) determining the level of the original amino acid sequence in the second sample; and

(iii) comparing the level obtained in (a) and (b) to give said ratio.

28. A method according to Claim 27, wherein said first and said second biological samples are the same sample.

29. A method for detecting any one of the antibodies of Claim 6 in a biological sample comprising the steps of:

(a) contacting said biological sample with any one of the amino acid sequences of Claim 3 or 4 thereby forming an antibody-antigen complex; and

(b) detecting said antibody-antigen complex

wherein the presence of said antibody-antigen complex correlates with the presence of the antibody in said biological sample.

30. A method for detecting the level of any one of the antibodies of Claim 6 in a biological sample comprising the steps of:

(i) contacting said biological sample with any one of the amino acid sequences of Claim 3;

(ii) detecting the amount of said antibody-antigen complex and normalizing said amount to provide the levels of said antibody in the sample.

For the Applicants,
REINHOLD COHN AND PARTNERS
By:

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gaggattgaa gttggaagtg tgaggtcagc ctgggcaatg tatcgagacc cctgtctcca 2340
aaacaataaa gggga 2355

<210> 37
<211> 497
<212> PRT
<213> Homo sapiens

<400> 37
Met Val Arg Ser Gly Asn Lys Ala Ala Val Val Leu Cys Met Asp Val
1   5   10   15

Gly Phe Thr Met Ser Asn Ser Ile Pro Gly Ile Glu Ser Pro Phe Glu
            20   25   30

Gln Ala Lys Lys Val Ile Thr Met Phe Val Gln Arg Gln Val Phe Ala
        35   40   45

Glu Asn Lys Asp Glu Ile Ala Leu Val Leu Phe Gly Thr Asp Gly Thr
    50   55   60

Asp Asn Pro Leu Ser Gly Gly Asp Gln Tyr Gln Asn Ile Thr Val His
65   70   75   80

Arg His Leu Met Leu Pro Asp Phe Asp Leu Leu Glu Asp Ile Glu Ser
                85   90   95

Lys Ile Gln Pro Gly Ser Gln Gln Ala Asp Phe Leu Asp Ala Leu Ile
            100   105   110

Val Ser Met Asp Val Ile Gln His Glu Thr Ile Gly Lys Lys Phe Glu
        115   120   125

Lys Arg His Ile Glu Ile Phe Thr Asp Leu Ser Ser Arg Phe Ser Lys
    130   135   140

Ser Gln Leu Asp Ile Ile Ile His Ser Leu Lys Lys Cys Asp Ile Ser
145   150   155   160

Leu Gln Phe Phe Leu Pro Phe Ser Leu Gly Lys Glu Asp Gly Ser Gly

165 170 175

Asp Arg Gly Asp Gly Pro Phe Arg Leu Gly Gly His Gly Pro Ser Phe
180 185 190

Pro Leu Lys Gly Ile Thr Glu Gln Gln Lys Glu Gly Leu Glu Ile Val
195 200 205

Lys Met Val Met Ile Ser Leu Glu Gly Glu Asp Gly Leu Asp Glu Ile
210 215 220

Tyr Ser Phe Ser Glu Ser Leu Arg Lys Leu Cys Val Phe Lys Lys Ile
225 230 235 240

Glu Arg His Ser Ile His Trp Pro Cys Arg Leu Thr Ile Gly Ser Asn
245 250 255

Leu Ser Ile Arg Ile Ala Ala Tyr Lys Ser Ile Leu Gln Glu Arg Val
260 265 270

Lys Lys Thr Trp Thr Val Val Asp Ala Lys Thr Leu Lys Lys Glu Asp
275 280 285

Ile Gln Lys Glu Thr Val Tyr Cys Leu Asn Asp Asp Asp Glu Thr Glu
290 295 300

Val Leu Lys Glu Asp Ile Ile Gln Gly Phe Arg Tyr Gly Ser Asp Ile
305 310 315 320

Val Pro Phe Ser Lys Val Asp Glu Glu Gln Met Lys Tyr Lys Ser Glu
325 330 335

Gly Lys Cys Phe Ser Val Leu Gly Phe Cys Lys Ser Ser Gln Val Gln
340 345 350

Arg Arg Phe Phe Met Gly Asn Gln Val Leu Lys Val Phe Ala Ala Arg
355 360 365

Asp Asp Glu Ala Ala Ala Val Ala Leu Ser Ser Leu Ile His Ala Leu
370 375 380

Asp Asp Leu Asp Met Val Ala Ile Val Arg Tyr Ala Tyr Asp Lys Arg
385 390 395 400

Ala Asn Pro Gln Val Gly Val Ala Phe Pro His Ile Lys His Asn Tyr
405 410 415

Glu Cys Leu Val Tyr Val Gln Leu Pro Phe Met Glu Asp Leu Arg Gln
420 425 430

Tyr Met Phe Ser Ser Leu Lys Asn Ser Lys Lys Tyr Ala Pro Thr Glu
435 440 445

Ala Gln Leu Asn Ala Val Asp Ala Leu Ile Asp Ser Met Ser Leu Ala
450 455 460

Lys Lys Asp Glu Lys Thr Asp Thr Leu Glu Asp Leu Phe Pro Thr Thr
465 470 475 480

Lys Ile Pro Asn Pro Arg Phe Gln Arg Leu Phe Gln Val Arg Glu Glu
485 490 495

Gly

<210> 38
<211> 521
<212> PRT
<213> Homo sapiens

<400> 38
Met Val Arg Ser Gly Asn Lys Ala Ala Val Val Leu Cys Met Asp Val
1 5 10 15

Gly Phe Thr Met Ser Asn Ser Ile Pro Gly Ile Glu Ser Pro Phe Glu
20 25 30

Gln Ala Lys Lys Val Ile Thr Met Phe Val Gln Arg Gln Val Phe Ala
35 40 45

Glu Asn Lys Asp Glu Ile Ala Leu Val Leu Phe Gly Thr Asp Gly Thr
50 55 60

Asp Asn Pro Leu Ser Gly Gly Asp Gln Tyr Gln Asn Ile Thr Val His
65 70 75 80

Arg His Leu Met Leu Pro Asp Phe Asp Leu Leu Glu Asp Ile Glu Ser
85 90 95

Lys Ile Gln Pro Gly Ser Gln Gln Ala Asp Phe Leu Asp Ala Leu Ile
100 105 110

Val Ser Met Asp Val Ile Gln His Glu Thr Ile Gly Lys Lys Phe Glu
115 120 125

Lys Arg His Ile Glu Ile Phe Thr Asp Leu Ser Ser Arg Phe Ser Lys
130 135 140

Ser Gln Leu Asp Ile Ile Ile His Ser Leu Lys Lys Cys Asp Ile Ser
145 150 155 160

Leu Gln Phe Phe Leu Pro Phe Ser Leu Gly Lys Glu Asp Gly Ser Gly
165 170 175

Asp Arg Gly Asp Gly Pro Phe Arg Leu Gly Gly His Gly Pro Ser Phe
180 185 190

Pro Leu Lys Gly Ile Thr Glu Gln Gln Lys Glu Gly Leu Glu Ile Val
195 200 205

Lys Met Val Met Ile Ser Leu Glu Gly Glu Asp Gly Leu Asp Glu Ile
210 215 220

Tyr Ser Phe Ser Glu Ser Leu Arg Lys Leu Cys Val Phe Lys Lys Ile
225 230 235 240

Glu Arg His Ser Ile His Trp Pro Cys Arg Leu Thr Ile Gly Ser Asn
245 250 255

Leu Ser Ile Arg Ile Ala Ala Tyr Lys Ser Ile Leu Gln Glu Arg Val

260 265 270

Lys Lys Thr Trp Thr Val Val Asp Ala Lys Thr Leu Lys Lys Glu Asp
275 280 285

Ile Gln Lys Glu Thr Val Tyr Cys Leu Asn Asp Asp Asp Glu Thr Glu
290 295 300

Leu Asn Pro Pro Ala Glu Val Thr Thr Lys Ser Gln Ile Pro Leu Ser
305 310 315 320

Lys Ile Lys Thr Leu Phe Pro Leu Ile Glu Ala Lys Lys Lys Asp Gln
325 330 335

Val Thr Ala Gln Glu Ile Phe Gln Asp Asn His Glu Asp Gly Pro Thr
340 345 350

Ala Lys Lys Leu Lys Thr Glu Gln Gly Gly Ala His Phe Ser Val Ser
355 360 365

Ser Leu Ala Glu Gly Ser Val Thr Ser Val Gly Ser Val Asn Pro Ala
370 375 380

Glu Asn Phe Arg Val Leu Val Lys Gln Lys Lys Ala Ser Phe Glu Glu
385 390 395 400

Ala Ser Asn Gln Leu Ile Asn His Ile Glu Gln Phe Leu Asp Thr Asn
405 410 415

Glu Thr Pro Tyr Phe Met Lys Ser Ile Asp Cys Ile Arg Ala Phe Arg
420 425 430

Glu Glu Ala Ile Lys Phe Ser Glu Glu Gln Arg Phe Asn Asn Phe Leu
435 440 445

Lys Ala Leu Gln Glu Lys Val Glu Ile Lys Gln Leu Asn His Phe Trp
450 455 460

Glu Ile Val Val Gln Asp Gly Ile Thr Leu Ile Thr Lys Glu Glu Ala
465 470 475 480

Ser Gly Ser Ser Val Thr Ala Glu Glu Ala Lys Lys Phe Leu Ala Pro
485 490 495

Lys Asp Lys Pro Ser Gly Asp Thr Ala Ala Val Phe Glu Glu Gly Gly
500 505 510

Asp Val Asp Asp Leu Leu Asp Met Ile
515 520

<210> 39
<211> 437
<212> PRT
<213> Homo sapiens

<400> 39
Met Gly Cys Gly Cys Ser Ser His Pro Glu Asp Asp Trp Met Glu Asn
1 5 10 15

Ile Asp Val Cys Glu Asn Cys His Tyr Pro Ile Val Pro Leu Asp Gly
20 25 30

Lys Gly Thr Leu Leu Ile Arg Asn Gly Ser Glu Val Arg Asp Pro Leu
35 40 45

Val Thr Tyr Glu Gly Ser Asn Pro Pro Ala Ser Pro Leu Gln Asp Asn
50 55 60

Leu Val Ile Ala Leu His Ser Tyr Glu Pro Ser His Asp Gly Asp Leu
65 70 75 80

Gly Phe Glu Lys Gly Glu Gln Leu Arg Ile Leu Glu Gln Ser Gly Glu
85 90 95

Trp Trp Lys Ala Gln Ser Leu Thr Thr Gly Gln Glu Gly Phe Ile Pro
100 105 110

Phe Asn Phe Val Ala Lys Ala Asn Ser Leu Glu Pro Glu Pro Trp Phe
115 120 125

Phe Lys Asn Leu Ser Arg Lys Asp Ala Glu Arg Gln Leu Leu Ala Pro
130 135 140

Gly Asn Thr His Gly Ser Phe Leu Ile Arg Glu Ser Glu Ser Thr Ala
145 150 155 160

Gly Ser Phe Ser Leu Ser Val Arg Asp Phe Asp Gln Asn Gln Gly Glu
165 170 175

Val Val Lys His Tyr Lys Ile Arg Asn Leu Asp Asn Gly Gly Phe Tyr
180 185 190

Ile Ser Pro Arg Ile Thr Phe Pro Gly Leu His Glu Leu Val Arg His
195 200 205

Tyr Thr Asn Ala Ser Asp Gly Leu Cys Thr Arg Leu Ser Arg Pro Cys
210 215 220

Gln Thr Gln Lys Pro Gln Lys Pro Trp Trp Glu Asp Glu Trp Glu Val
225 230 235 240

Pro Arg Glu Thr Leu Lys Leu Val Glu Arg Leu Gly Ala Gly Gln Phe
245 250 255

Gly Glu Val Trp Met Gly Tyr Tyr Asn Gly His Thr Lys Val Ala Val
260 265 270

Lys Ser Leu Lys Gln Gly Ser Met Ser Pro Asp Ala Phe Leu Ala Glu
275 280 285

Ala Asn Leu Met Lys Gln Leu Gln His Gln Arg Leu Val Arg Leu Tyr
290 295 300

Ala Val Val Thr Gln Glu Pro Ile Tyr Ile Ile Thr Glu Tyr Met Glu
305 310 315 320

Asn Gly Ser Leu Val Asp Phe Leu Lys Thr Pro Ser Gly Ile Lys Leu
325 330 335

Thr Ile Asn Lys Leu Leu Asp Met Ala Ala Gln Ile Ala Glu Gly Met

340 345 350

Ala Phe Ile Glu Glu Arg Asn Tyr Ile His Arg Asp Leu Arg Ala Ala
355 360 365

Asn Ile Leu Val Ser Asp Thr Leu Ser Cys Lys Ile Ala Asp Phe Gly
370 375 380

Leu Ala Arg Leu Ile Glu Asp Ile His His Gln Val Arg Cys Val Val
385 390 395 400

Phe Trp Asp Pro Ala Asp Gly Asn Cys His Pro Arg Pro His Pro Leu
405 410 415

Pro Arg Asp Asp Gln Pro Gly Gly Asp Ser Glu Pro Gly Ala Arg Leu
420 425 430

Pro His Gly Ala Pro
435

<210> 40
<211> 567
<212> PRT
<213> Homo sapiens

<400> 40
Met Gly Cys Gly Cys Ser Ser His Pro Glu Asp Asp Trp Met Glu Asn
1 5 10 15

Ile Asp Val Cys Glu Asn Cys His Tyr Pro Ile Val Pro Leu Asp Gly
20 25 30

Lys Gly Thr Leu Leu Ile Arg Asn Gly Ser Glu Val Arg Asp Pro Leu
35 40 45

Val Thr Tyr Glu Gly Ser Asn Pro Pro Ala Ser Pro Leu Gln Gly Asp
50 55 60

Pro Arg Gln Gln Gly Leu Lys Asp Lys Ala Cys Gly Ser Leu Ala Val
65 70 75 80

Gly Phe His Leu Ser Pro Thr Tyr Phe Leu Pro Gly Leu Ala Phe Leu
85 90 95

Val Pro His Pro Val Thr Pro Gly Phe Leu Pro Ile Pro Ala Arg Phe
100 105 110

Ser Leu Thr Pro Leu Val Phe Thr Asp Asn Leu Val Ile Ala Leu His
115 120 125

Ser Tyr Glu Pro Ser His Asp Gly Asp Leu Gly Phe Glu Lys Gly Glu
130 135 140

Gln Leu Arg Ile Leu Glu Gln Ser Gly Glu Trp Trp Lys Ala Gln Ser
145 150 155 160

Leu Thr Thr Gly Gln Glu Gly Phe Ile Pro Phe Asn Phe Val Ala Lys
165 170 175

Ala Asn Ser Leu Glu Pro Glu Pro Trp Phe Phe Lys Asn Leu Ser Arg
180 185 190

Lys Asp Ala Glu Arg Gln Leu Leu Ala Pro Gly Asn Thr His Gly Ser
195 200 205

Phe Leu Ile Arg Glu Ser Glu Ser Thr Ala Gly Ser Phe Ser Leu Ser
210 215 220

Val Arg Asp Phe Asp Gln Asn Gln Gly Glu Val Val Lys His Tyr Lys
225 230 235 240

Ile Arg Asn Leu Asp Asn Gly Gly Phe Tyr Ile Ser Pro Arg Ile Thr
245 250 255

Phe Pro Gly Leu His Glu Leu Val Arg His Tyr Thr Asn Ala Ser Asp
260 265 270

Gly Leu Cys Thr Arg Leu Ser Arg Pro Cys Gln Thr Gln Lys Pro Gln
275 280 285

Lys Pro Trp Trp Glu Asp Glu Trp Glu Val Pro Arg Glu Thr Leu Lys
290 295 300

Leu Val Glu Arg Leu Gly Ala Gly Gln Phe Gly Glu Val Trp Met Gly
305 310 315 320

Tyr Tyr Asn Gly His Thr Lys Val Ala Val Lys Ser Leu Lys Gln Gly
325 330 335

Ser Met Ser Pro Asp Ala Phe Leu Ala Glu Ala Asn Leu Met Lys Gln
340 345 350

Leu Gln His Gln Arg Leu Val Arg Leu Tyr Ala Val Val Thr Gln Glu
355 360 365

Pro Ile Tyr Ile Ile Thr Glu Tyr Met Glu Asn Gly Ser Leu Val Asp
370 375 380

Phe Leu Lys Thr Pro Ser Gly Ile Lys Leu Thr Ile Asn Lys Leu Leu
385 390 395 400

Asp Met Ala Ala Gln Ile Ala Glu Gly Met Ala Phe Ile Glu Glu Arg
405 410 415

Asn Tyr Ile His Arg Asp Leu Arg Ala Ala Asn Ile Leu Val Ser Asp
420 425 430

Thr Leu Ser Cys Lys Ile Ala Asp Phe Gly Leu Ala Arg Leu Ile Glu
435 440 445

Asp Asn Glu Tyr Thr Ala Arg Glu Gly Ala Lys Phe Pro Ile Lys Trp
450 455 460

Thr Ala Pro Glu Ala Ile Asn Tyr Gly Thr Phe Thr Ile Lys Ser Asp
465 470 475 480

Val Trp Ser Phe Gly Ile Leu Leu Thr Glu Ile Val Thr His Gly Arg
485 490 495

Ile Pro Tyr Pro Gly Met Thr Asn Pro Glu Val Ile Gln Asn Leu Glu

500 505 510

Arg Gly Tyr Arg Met Val Arg Pro Asp Asn Cys Pro Glu Glu Leu Tyr
515 520 525

Gln Leu Met Arg Leu Cys Trp Lys Glu Arg Pro Glu Asp Arg Pro Thr
530 535 540

Phe Asp Tyr Leu Arg Ser Val Leu Glu Asp Phe Phe Thr Ala Thr Glu
545 550 555 560

Gly Gln Tyr Gln Pro Gln Pro
565

<210> 41
<211> 192
<212> PRT
<213> Homo sapiens

<400> 41
Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1 5 10 15

Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
20 25 30

Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
35 40 45

Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu
50 55 60

Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu
65 70 75 80

Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His
85 90 95

Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp
100 105 110

Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu
115 120 125

Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu
130 135 140

Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly
145 150 155 160

Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg
165 170 175

Pro Asp Ile Gln Val Asn Pro Leu Thr Asp Thr Pro Asp Gly Ser Asp
180 185 190

<210> 42
<211> 109
<212> PRT
<213> Homo sapiens

<400> 42
Met Glu Leu Gly Leu Pro Gln Val Pro Pro Ala Val Asp Ala Glu Leu
1 5 10 15

Leu Cys Arg Phe Val Asp Arg Gly Leu Pro Tyr Pro Asp Val Ser Ser
20 25 30

Ala Asn Thr Pro Pro Ala Val Gly Leu Ser Pro Pro Thr Pro Tyr Phe
35 40 45

Glu Pro Cys Ala Leu Pro Ser Pro His Arg His Gln Leu Ala Glu Ala
50 55 60

Ile Pro Cys Thr Leu Ala Val Ser Asn Pro His Thr Asp Ala Trp Lys
65 70 75 80

Ser His Gly Leu Val Glu Val Ala Ser Tyr Cys Glu Glu Ser Arg Gly
85 90 95

Asn Asn Gln Trp Val Pro Tyr Ile Ser Leu Gln Glu Arg
100 105

<210> 43
<211> 331
<212> PRT
<213> Homo sapiens

<400> 43
Met Arg Ala Arg Pro Gln Val Cys Glu Ala Leu Leu Phe Ala Leu Ala
1 5 10 15

Leu Gln Thr Gly Val Cys Tyr Gly Ile Lys Trp Leu Ala Leu Ser Lys
20 25 30

Thr Pro Ser Ala Leu Ala Leu Asn Gln Thr Gln His Cys Lys Gln Leu
35 40 45

Glu Gly Leu Val Ser Ala Gln Val Gln Leu Cys Arg Ser Asn Leu Glu
50 55 60

Leu Met His Thr Val Val His Ala Ala Arg Glu Val Met Lys Ala Cys
65 70 75 80

Arg Arg Ala Phe Ala Asp Met Arg Trp Asn Cys Ser Ser Ile Glu Leu
85 90 95

Ala Pro Asn Tyr Leu Leu Asp Leu Glu Arg Gly Thr Arg Glu Ser Ala
100 105 110

Phe Val Tyr Ala Leu Ser Ala Ala Ala Ile Ser His Ala Ile Ala Arg
115 120 125

Ala Cys Thr Ser Gly Asp Leu Pro Gly Cys Ser Cys Gly Pro Val Pro
130 135 140

Gly Glu Pro Pro Gly Pro Gly Asn Arg Trp Gly Arg Cys Ala Asp Asn
145 150 155 160

Leu Ser Tyr Gly Leu Leu Met Gly Ala Lys Phe Ser Asp Ala Pro Met
165 170 175

Lys Val Lys Lys Thr Gly Ser Gln Ala Asn Lys Leu Met Arg Leu His
180 185 190

Asn Ser Glu Val Gly Arg Gln Ala Leu Arg Ala Ser Leu Glu Met Lys
195 200 205

Cys Lys Cys His Gly Val Ser Gly Ser Cys Ser Ile Arg Thr Cys Trp
210 215 220

Lys Gly Leu Gln Glu Leu Gln Asp Val Ala Ala Asp Leu Lys Thr Arg
225 230 235 240

Tyr Leu Ser Ala Thr Lys Val Val His Arg Pro Met Gly Thr Arg Lys
245 250 255

His Leu Val Pro Lys Asp Leu Asp Ile Arg Pro Val Lys Asp Ser Glu
260 265 270

Leu Val Tyr Leu Gln Ser Ser Pro Asp Phe Cys Met Lys Asn Glu Lys
275 280 285

Val Gly Ser His Gly Thr Gln Asp Arg Gln Cys Asn Lys Thr Ser Asn
290 295 300

Gly Ser Asp Ser Cys Asp Leu Met Cys Cys Tyr Val Thr Cys Arg Arg
305 310 315 320

Cys Glu Arg Thr Val Glu Arg Tyr Val Cys Lys
325 330

<210> 44
<211> 237
<212> PRT
<213> Homo sapiens

<400> 44
Met Arg Ala Arg Pro Gln Val Cys Glu Ala Leu Leu Phe Ala Leu Ala
1 5 10 15

Leu Gln Thr Gly Val Cys Tyr Gly Ile Lys Trp Leu Ala Leu Ser Lys
20 25 30

Thr Pro Ser Ala Leu Ala Leu Asn Gln Thr Gln His Cys Lys Gln Leu
35 40 45

Glu Gly Leu Val Ser Ala Gln Val Gln Leu Cys Arg Ser Asn Leu Glu
50 55 60

Leu Met His Thr Val Val His Ala Ala Arg Glu Val Met Lys Ala Cys
65 70 75 80

Arg Arg Ala Phe Ala Asp Met Arg Trp Asn Cys Ser Ser Ile Glu Leu
85 90 95

Ala Pro Asn Tyr Leu Leu Asp Leu Glu Arg Gly Thr Arg Glu Ser Ala
100 105 110

Phe Val Tyr Ala Ala Ala Asp Leu Lys Thr Arg Tyr Leu Ser Ala Thr
115 120 125

Lys Val Val His Arg Pro Met Gly Thr Arg Lys His Leu Val Pro Lys
130 135 140

Asp Leu Asp Ile Arg Pro Val Lys Asp Ser Glu Leu Val Tyr Leu Gln
145 150 155 160

Ser Ser Pro Asp Phe Cys Met Lys Asn Glu Lys Val Gly Ser His Gly
165 170 175

Thr Gln Asp Arg Gln Cys Asn Lys Thr Ser Asn Gly Ser Asp Ser Cys
180 185 190

Asp Leu Met Cys Cys Gly Arg Gly Tyr Asn Pro Tyr Thr Asp Arg Val
195 200 205

Val Glu Arg Cys His Cys Lys Tyr His Trp Cys Cys Tyr Val Thr Cys
210 215 220

Arg Arg Cys Glu Arg Thr Val Glu Arg Tyr Val Cys Lys
225 230 235

<210> 45
<211> 615
<212> PRT
<213> Homo sapiens

<400> 45
Met Ser Pro Phe Leu Arg Ile Gly Leu Ser Asn Phe Asp Cys Gly Ser
1 5 10 15

Cys Gln Ser Cys Gln Gly Glu Ala Val Asn Pro Tyr Cys Ala Val Leu
20 25 30

Val Lys Glu Tyr Val Glu Ser Glu Asn Gly Gln Met Tyr Ile Gln Lys
35 40 45

Lys Pro Thr Met Tyr Pro Pro Trp Asp Ser Thr Phe Asp Ala His Ile
50 55 60

Asn Lys Gly Arg Val Met Gln Ile Ile Val Lys Gly Lys Asn Val Asp
65 70 75 80

Leu Ile Ser Glu Thr Thr Val Glu Leu Tyr Ser Leu Ala Glu Arg Cys
85 90 95

Arg Lys Asn Asn Gly Lys Thr Glu Ile Trp Leu Glu Leu Lys Pro Gln
100 105 110

Gly Arg Met Leu Met Asn Ala Arg Tyr Phe Leu Glu Met Ser Asp Thr

115 120 125

Lys Asp Met Asn Glu Phe Glu Thr Glu Gly Phe Phe Ala Leu His Gln
130 135 140

Arg Arg Gly Ala Ile Lys Gln Ala Lys Val His His Val Lys Cys His
145 150 155 160

Glu Phe Thr Ala Thr Phe Phe Pro Gln Pro Thr Phe Cys Ser Val Cys
165 170 175

His Glu Phe Val Trp Gly Leu Asn Lys Gln Gly Tyr Gln Cys Arg Gln
180 185 190

Cys Asn Ala Ala Ile His Lys Lys Cys Ile Asp Lys Val Ile Ala Lys
195 200 205

Cys Thr Gly Ser Ala Ile Asn Ser Arg Glu Thr Met Phe His Lys Glu
210 215 220

Arg Phe Lys Ile Asp Met Pro His Arg Phe Lys Val Tyr Asn Tyr Lys
225 230 235 240

Ser Pro Thr Phe Cys Glu His Cys Gly Thr Leu Leu Trp Gly Leu Ala
245 250 255

Arg Gln Gly Leu Lys Cys Asp Ala Cys Gly Met Asn Val His His Arg
260 265 270

Cys Gln Thr Lys Val Ala Asn Leu Cys Gly Ile Asn Gln Lys Leu Met
275 280 285

Ala Glu Ala Leu Ala Met Ile Glu Ser Thr Gln Gln Ala Arg Cys Leu
290 295 300

Arg Asp Thr Glu Gln Ile Phe Arg Glu Gly Pro Val Glu Ile Gly Leu
305 310 315 320

Pro Cys Ser Ile Lys Asn Glu Ala Arg Pro Pro Cys Leu Pro Thr Pro
325 330 335

Gly Lys Arg Glu Pro Gln Gly Ile Ser Trp Glu Ser Pro Leu Asp Glu
340 345 350

Val Asp Lys Met Cys His Leu Pro Glu Pro Glu Leu Asn Lys Glu Arg
355 360 365

Pro Ser Leu Gln Ile Lys Leu Lys Ile Glu Asp Phe Ile Leu His Lys
370 375 380

Met Leu Gly Lys Gly Ser Phe Gly Lys Val Phe Leu Ala Glu Phe Lys
385 390 395 400

Lys Thr Asn Gln Phe Phe Ala Ile Lys Ala Leu Lys Lys Asp Val Val
405 410 415

Leu Met Asp Asp Asp Val Glu Cys Thr Met Val Glu Lys Arg Val Leu
420 425 430

Ser Leu Ala Trp Glu His Pro Phe Leu Thr His Met Phe Cys Thr Phe
435 440 445

Gln Thr Lys Glu Asn Leu Phe Phe Val Met Glu Tyr Leu Asn Gly Gly
    450   455   460

Asp Leu Met Tyr His Ile Gln Ser Cys His Lys Phe Asp Leu Ser Arg
465   470   475   480

Ala Thr Phe Tyr Ala Ala Glu Ile Ile Leu Gly Leu Gln Phe Leu His
                485   490   495

Ser Lys Gly Ile Val Tyr Arg Asp Leu Lys Leu Asp Asn Ile Leu Leu
            500   505   510

Asp Lys Asp Gly His Ile Lys Ile Ala Asp Phe Gly Met Cys Lys Glu
        515   520   525

Asn Met Leu Gly Asp Ala Lys Thr Asn Thr Phe Cys Gly Thr Pro Asp
    530   535   540

Tyr Ile Ala Pro Glu Ile Leu Leu Gly Gln Lys Tyr Asn His Ser Val
545   550   555   560

Asp Trp Trp Ser Phe Gly Val Leu Leu Tyr Glu Met Leu Ile Gly Gln
                565   570   575

Ser Pro Phe His Gly Gln Asp Glu Glu Glu Leu Phe His Ser Ile Arg
            580   585   590

Met Asp Asn Pro Phe Tyr Pro Arg Trp Leu Glu Lys Glu Ala Lys Asp
        595   600   605

Leu Leu Val Lys Val Arg Ser
    610   615

<210> 46
<211> 292
<212> PRT
<213> Homo sapiens

<400> 46
Met Pro Ile Thr Arg Met Arg Met Arg Pro Trp Leu Glu Met Gln Ile
1   5   10   15

Asn Ser Asn Gln Ile Pro Gly Leu Ile Trp Ile Asn Lys Glu Glu Met
            20   25   30

Ile Phe Gln Ile Pro Trp Lys His Ala Ala Lys His Gly Trp Asp Ile
        35   40   45

Asn Lys Asp Ala Cys Leu Phe Arg Ser Trp Ala Ile His Thr Gly Arg
    50   55   60

Tyr Lys Ala Gly Glu Lys Glu Pro Asp Pro Lys Thr Trp Lys Ala Asn
65   70   75   80

Phe Arg Cys Ala Met Asn Ser Leu Pro Asp Ile Glu Glu Val Lys Asp
                85   90   95

Gln Ser Arg Asn Lys Gly Ser Ser Ala Val Arg Val Tyr Arg Met Leu

100 105 110

Pro Pro Leu Thr Lys Asn Gln Arg Lys Glu Arg Lys Ser Lys Ser Ser
115 120 125

Arg Asp Ala Lys Ser Lys Ala Lys Arg Lys Ser Cys Gly Asp Ser Ser
130 135 140

Pro Asp Thr Phe Ser Asp Gly Leu Ser Ser Ser Thr Leu Pro Asp Asp
145 150 155 160

His Ser Ser Tyr Thr Val Pro Gly Tyr Met Gln Asp Leu Glu Val Glu
165 170 175

Gln Ala Leu Thr Pro Ala Leu Ser Pro Cys Ala Val Ser Ser Thr Leu
180 185 190

Pro Asp Trp His Ile Pro Val Glu Val Val Pro Asp Ser Thr Ser Asp
195 200 205

Leu Tyr Asn Phe Gln Val Ser Pro Met Pro Ser Thr Ser Glu Ala Thr
210 215 220

Thr Asp Glu Asp Glu Glu Gly Lys Leu Pro Glu Asp Ile Met Lys Leu
225 230 235 240

Leu Glu Gln Ser Glu Trp Gln Pro Thr Asn Val Asp Gly Lys Gly Tyr
245 250 255

Leu Leu Asn Glu Pro Gly Val Gln Pro Thr Ser Val Tyr Gly Asp Phe
260 265 270

Ser Cys Lys Glu Glu Pro Glu Ile Asp Ser Pro Gly Gly Lys Lys Ala
275 280 285

Pro Gly Ser Leu
290

<210> 47
<211> 702
<212> PRT
<213> Homo sapiens

<400> 47
Met Trp Ser Trp Lys Cys Leu Leu Phe Trp Ala Val Leu Val Thr Ala
1 5 10 15

Thr Leu Cys Thr Ala Arg Pro Ser Pro Thr Leu Pro Glu Gln Ala Gln
20 25 30

Pro Trp Gly Ala Pro Val Glu Val Glu Ser Phe Leu Val His Pro Gly
35 40 45

Asp Leu Leu Gln Leu Arg Cys Arg Leu Arg Asp Asp Val Gln Ser Ile
50 55 60

Asn Trp Leu Arg Asp Gly Val Gln Leu Ala Glu Ser Asn Arg Thr Arg
65 70 75 80

Ile Thr Gly Glu Glu Val Glu Val Gln Asp Ser Val Pro Ala Asp Ser
85 90 95

Gly Leu Tyr Ala Cys Val Thr Ser Ser Pro Ser Gly Ser Asp Thr Thr
100 105 110

Tyr Phe Ser Val Asn Val Ser Asp Ala Leu Pro Ser Ser Glu Asp Asp
115 120 125

Asp Asp Asp Asp Asp Ser Ser Ser Glu Glu Lys Glu Thr Asp Asn Thr
130 135 140

Lys Pro Asn Arg Met Pro Val Ala Pro Tyr Trp Thr Ser Pro Glu Lys
145 150 155 160

Met Glu Lys Lys Leu His Ala Val Pro Ala Ala Lys Thr Val Lys Phe
165 170 175

Lys Cys Pro Ser Ser Gly Thr Pro Asn Pro Thr Leu Arg Trp Leu Lys
180 185 190

Asn Gly Lys Glu Phe Lys Pro Asp His Arg Ile Gly Gly Tyr Lys Val
195 200 205

Arg Tyr Ala Thr Trp Ser Ile Ile Met Asp Ser Val Val Pro Ser Asp
210 215 220

Lys Gly Asn Tyr Thr Cys Ile Val Glu Asn Glu Tyr Gly Ser Ile Asn
225 230 235 240

His Thr Tyr Gln Leu Asp Val Val Glu Arg Ser Pro His Arg Pro Ile
245 250 255

Leu Gln Ala Gly Leu Pro Ala Asn Lys Thr Val Ala Leu Gly Ser Asn
260 265 270

Val Glu Phe Met Cys Lys Val Tyr Ser Asp Pro Gln Pro His Ile Gln
275 280 285

Trp Leu Lys His Ile Glu Val Asn Gly Ser Lys Ile Gly Pro Asp Asn
290 295 300

Leu Pro Tyr Val Gln Ile Leu Lys Thr Ala Gly Val Asn Thr Thr Asp
305 310 315 320

Lys Glu Met Glu Val Leu His Leu Arg Asn Val Ser Phe Glu Asp Ala
325 330 335

Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu Ser His His
340 345 350

Ser Ala Trp Leu Thr Val Leu Glu Ala Leu Glu Glu Arg Pro Ala Val
355 360 365

Met Thr Ser Pro Leu Tyr Leu Glu Ile Ile Ile Tyr Cys Thr Gly Ala
370 375 380

Phe Leu Ile Ser Cys Met Val Gly Ser Val Ile Val Tyr Lys Met Lys
385 390 395 400

Ser Gly Thr Lys Lys Ser Asp Phe His Ser Gln Met Ala Val His Lys

405 410 415

Leu Ala Lys Ser Ile Pro Leu Arg Arg Gln Val Thr Val Ser Ala Asp
420 425 430

Ser Ser Ala Ser Met Asn Ser Gly Val Leu Leu Val Arg Pro Ser Arg
435 440 445

Leu Ser Ser Ser Gly Thr Pro Met Leu Ala Gly Val Ser Glu Tyr Glu
450 455 460

Leu Pro Glu Asp Pro Arg Trp Glu Leu Pro Arg Asp Arg Leu Val Leu
465 470 475 480

Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val Val Leu Ala Glu
485 490 495

Ala Ile Gly Leu Asp Lys Asp Lys Pro Asn Arg Val Thr Lys Val Ala
500 505 510

Val Lys Met Leu Lys Ser Asp Ala Thr Glu Lys Asp Leu Ser Asp Leu
515 520 525

Ile Ser Glu Met Glu Met Met Lys Met Ile Gly Lys His Lys Asn Ile
530 535 540

Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu Tyr Val Ile
545 550 555 560

Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu Gln Ala Arg
565 570 575

Arg Pro Pro Gly Leu Glu Tyr Cys Tyr Asn Pro Ser His Asn Pro Glu
580 585 590

Glu Gln Leu Ser Ser Lys Asp Leu Val Ser Cys Ala Tyr Gln Val Ala
595 600 605

Arg Gly Met Glu Tyr Leu Ala Ser Lys Lys Cys Ile His Arg Asp Leu
610 615 620

Ala Ala Arg Asn Val Leu Val Thr Glu Asp Asn Val Met Lys Ile Ala
625 630 635 640

Asp Phe Gly Leu Ala Arg Asp Ile His His Ile Asp Tyr Tyr Lys Lys
645 650 655

Thr Thr Asn Gly Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ala Leu
660 665 670

Phe Asp Arg Ile Tyr Thr His Gln Ser Asp Val Trp Ser Phe Gly Val
675 680 685

Pro His Thr Pro Val Cys Leu Trp Arg Asn Phe Ser Ser Cys
690 695 700

<210> 48
<211> 295
<212> PRT

<213> Homo sapiens

<400> 48

Met Pro Lys Arg Gly Lys Lys Gly Ala Val Ala Glu Asp Gly Asp Glu
1   5   10   15

Leu Arg Thr Glu Pro Glu Ala Lys Lys Ser Lys Thr Ala Ala Lys Lys
            20   25   30

Asn Asp Lys Glu Ala Ala Gly Glu Gly Pro Ala Leu Tyr Glu Asp Pro
        35   40   45

Pro Asp Gln Lys Thr Ser Pro Ser Gly Lys Pro Ala Thr Leu Lys Ile
    50   55   60

Cys Ser Trp Asn Val Asp Gly Leu Arg Ala Trp Ile Lys Lys Lys Gly
65   70   75   80

Leu Asp Trp Val Lys Glu Glu Ala Pro Asp Ile Leu Cys Leu Gln Glu
                85   90   95

Thr Lys Cys Ser Glu Asn Lys Leu Pro Ala Glu Leu Gln Glu Leu Pro
            100   105   110

Gly Leu Ser His Gln Tyr Trp Ser Ala Pro Ser Asp Lys Glu Gly Tyr
        115   120   125

Ser Gly Val Gly Leu Leu Ser Arg Gln Cys Pro Leu Lys Val Ser Tyr
    130   135   140

Gly Ile Ala Tyr Val Pro Asn Ala Gly Arg Gly Leu Val Arg Leu Glu
145   150   155   160

Tyr Arg Gln Arg Trp Asp Glu Ala Phe Arg Lys Phe Leu Lys Gly Leu
                165   170   175

Ala Ser Arg Lys Pro Leu Val Leu Cys Gly Asp Leu Asn Val Ala His
            180   185   190

Glu Glu Ile Asp Leu Arg Asn Pro Lys Gly Asn Lys Lys Asn Ala Gly
        195   200   205

Phe Thr Pro Gln Glu Arg Gln Gly Phe Gly Glu Leu Leu Gln Ala Val
    210   215   220

Pro Leu Ala Asp Ser Phe Arg His Leu Tyr Pro Asn Thr Pro Tyr Ala
225   230   235   240

Tyr Thr Phe Trp Thr Tyr Met Met Asn Ala Arg Ser Lys Asn Val Gly
                245   250   255

Trp Arg Leu Asp Tyr Phe Leu Leu Ser His Ser Leu Leu Pro Ala Leu
            260   265   270

Cys Asp Ser Lys Ile Arg Ser Lys Ala Leu Gly Ser Asp His Cys Pro
        275   280   285

Ile Thr Leu Tyr Leu Ala Leu
    290   295

<210> 49
<211> 342
<212> PRT
<213> Homo sapiens

<400> 49
Met Pro Lys Arg Gly Lys Lys Gly Ala Val Ala Glu Asp Gly Asp Glu
1   5   10   15

Leu Arg Thr Gly Lys Gly Met Lys Ser Ala Leu Leu Pro Arg Asn Cys
            20   25   30

Gly Gly Gly Val Cys His Ser Leu Asp Val Arg Glu Pro Glu Ala Lys
        35   40   45

Lys Ser Lys Thr Ala Ala Lys Lys Asn Asp Lys Glu Ala Ala Gly Glu
    50   55   60

Gly Pro Ala Leu Tyr Glu Asp Pro Pro Asp Gln Lys Thr Ser Pro Ser
65   70   75   80

Gly Lys Pro Ala Thr Leu Lys Ile Cys Ser Trp Asn Val Asp Gly Leu
                85   90   95

Arg Ala Trp Ile Lys Lys Lys Gly Leu Asp Trp Val Lys Glu Glu Ala
            100   105   110

Pro Asp Ile Leu Cys Leu Gln Glu Thr Lys Cys Ser Glu Asn Lys Leu
        115   120   125

Pro Ala Glu Leu Gln Glu Leu Pro Gly Leu Ser His Gln Tyr Trp Ser
    130   135   140

Ala Pro Ser Asp Lys Glu Gly Tyr Ser Gly Val Gly Leu Leu Ser Arg
145   150   155   160

Gln Cys Pro Leu Lys Val Ser Tyr Gly Ile Gly Asp Glu Glu His Asp
                165   170   175

Gln Glu Gly Arg Val Ile Val Ala Glu Phe Asp Ser Phe Val Leu Val
            180   185   190

Thr Ala Tyr Val Pro Asn Ala Gly Arg Gly Leu Val Arg Leu Glu Tyr
        195   200   205

Arg Gln Arg Trp Asp Glu Ala Phe Arg Lys Phe Leu Lys Gly Leu Ala
    210   215   220

Ser Arg Lys Pro Leu Val Leu Cys Gly Asp Leu Asn Val Ala His Glu
225   230   235   240

Glu Ile Asp Leu Arg Asn Pro Lys Gly Asn Lys Lys Asn Ala Gly Phe
                245   250   255

Thr Pro Gln Glu Arg Gln Gly Phe Gly Glu Leu Leu Gln Ala Val Pro
            260   265   270

Leu Ala Asp Ser Phe Arg His Leu Tyr Pro Asn Thr Pro Tyr Ala Tyr
        275   280   285

Thr Phe Trp Thr Tyr Met Met Asn Ala Arg Ser Lys Asn Val Gly Trp
    290   295   300

Arg Leu Asp Tyr Phe Leu Leu Ser His Ser Leu Leu Pro Ala Leu Cys
305   310   315   320

Asp Ser Lys Ile Arg Ser Lys Ala Leu Gly Ser Asp His Cys Pro Ile
                325   330   335

Thr Leu Tyr Leu Ala Leu
            340

<210> 50
<211> 305
<212> PRT
<213> Homo sapiens

<400> 50
Met Phe Gln Ala Ala Glu Arg Pro Gln Glu Trp Ala Met Glu Gly Pro
1   5   10   15

Arg Asp Gly Leu Lys Lys Glu Arg Leu Leu Asp Asp Arg His Asp Ser
            20   25   30

Gly Leu Asp Ser Met Lys Asp Glu Glu Tyr Glu Gln Met Val Lys Glu
        35   40   45

Leu Gln Glu Ile Arg Leu Glu Pro Gln Glu Val Pro Arg Gly Ser Glu
    50   55   60

Pro Trp Lys Gln Gln Leu Thr Glu Asp Gly Asp Ser Phe Leu His Leu
65   70   75   80

Ala Ile Ile His Glu Glu Lys Ala Leu Thr Met Glu Val Ile Arg Gln
                85   90   95

Val Lys Gly Asp Leu Ala Phe Leu Asn Phe Gln Asn Asn Leu Gln Gln
            100   105   110

Thr Pro Leu His Leu Ala Val Ile Thr Asn Gln Pro Glu Ile Ala Glu
        115   120   125

Ala Leu Leu Gly Ala Gly Cys Asp Pro Glu Leu Arg Asp Phe Arg Gly
    130   135   140

Asn Thr Pro Leu His Leu Ala Cys Glu Gln Gly Cys Leu Ala Ser Val
145   150   155   160

Gly Val Leu Thr Gln Ser Cys Thr Thr Pro His Leu His Ser Ile Leu
                165   170   175

Lys Ala Thr Asn Tyr Asn Gly His Thr Cys Leu His Leu Ala Ser Ile
            180   185   190

His Gly Tyr Leu Gly Ile Val Glu Leu Leu Val Ser Leu Gly Ala Asp
        195   200   205

Val Asn Ala Gln Glu Pro Cys Asn Gly Arg Thr Ala Leu His Leu Ala
    210   215   220

Val Asp Leu Gln Asn Pro Asp Leu Val Ser Leu Leu Leu Lys Cys Gly
225 230 235 240

Ala Asp Val Asn Arg Val Thr Tyr Gln Gly Tyr Ser Pro Tyr Gln Leu
245 250 255

Thr Trp Gly Arg Pro Ser Thr Arg Ile Gln Gln Gln Leu Gly Gln Leu
260 265 270

Thr Leu Glu Asn Leu Gln Met Leu Pro Glu Ser Glu Asp Glu Glu Ser
275 280 285

Tyr Asp Thr Glu Ser Glu Phe Thr Glu Phe Thr Glu Asp Glu Val Ser
290 295 300

Leu
305

<210> 51
<211> 289
<212> PRT
<213> Homo sapiens

<400> 51
Met Phe Gln Ala Ala Glu Arg Pro Gln Glu Trp Ala Met Glu Gly Pro
1 5 10 15

Arg Asp Gly Leu Lys Lys Glu Arg Leu Leu Asp Asp Arg His Asp Ser
20 25 30

Gly Leu Asp Ser Met Lys Asp Glu Glu Tyr Glu Gln Met Val Lys Glu
35 40 45

Leu Gln Glu Ile Arg Leu Glu Pro Gln Glu Val Pro Arg Gly Ser Glu
50 55 60

Pro Trp Lys Gln Gln Leu Thr Glu Asp Gly Asp Ser Phe Leu His Leu
65 70 75 80

Ala Ile Ile His Glu Glu Lys Ala Leu Thr Met Glu Val Ile Arg Gln
85 90 95

Val Lys Gly Asp Leu Ala Phe Leu Asn Phe Gln Asn Asn Leu Gln Gln
100 105 110

Thr Pro Leu His Leu Ala Val Ile Thr Asn Gln Pro Glu Ile Ala Glu
115 120 125

Ala Leu Leu Gly Ala Gly Cys Asp Pro Glu Leu Arg Asp Phe Arg Gly
130 135 140

Asn Thr Pro Leu His Leu Ala Cys Glu Gln Gly Cys Leu Ala Ser Val
145 150 155 160

Gly Val Leu Thr Gln Ser Cys Thr Thr Pro His Leu His Ser Ile Leu
165 170 175

Lys Ala Thr Asn Tyr Asn Gly Gln Glu Pro Cys Asn Gly Arg Thr Ala

180 185 190

Leu His Leu Ala Val Asp Leu Gln Asn Pro Asp Leu Val Ser Leu Leu
195 200 205

Leu Lys Cys Gly Ala Asp Val Asn Arg Val Thr Tyr Gln Gly Tyr Ser
210 215 220

Pro Tyr Gln Leu Thr Trp Gly Arg Pro Ser Thr Arg Ile Gln Gln Gln
225 230 235 240

Leu Gly Gln Leu Thr Leu Glu Asn Leu Gln Met Leu Pro Glu Ser Glu
245 250 255

Asp Glu Glu Ser Tyr Asp Thr Glu Ser Glu Phe Thr Glu Phe Thr Glu
260 265 270

Asp Glu Leu Pro Tyr Asp Asp Cys Val Phe Gly Gly Gln Arg Leu Thr
275 280 285

Leu

<210> 52
<211> 921
<212> PRT
<213> Homo sapiens

<400> 52
Met Ala Gly Ile Phe Tyr Phe Ala Leu Phe Ser Cys Leu Phe Gly Ile
1 5 10 15

Cys Asp Ala Val Thr Gly Ser Arg Val Tyr Pro Ala Asn Glu Val Thr
20 25 30

Leu Leu Asp Ser Arg Ser Val Gln Gly Glu Leu Gly Trp Ile Ala Ser
35 40 45

Pro Leu Glu Gly Gly Trp Glu Glu Val Ser Ile Met Asp Glu Lys Asn
50 55 60

Thr Pro Ile Arg Thr Tyr Gln Val Cys Asn Val Met Glu Pro Ser Gln
65 70 75 80

Asn Asn Trp Leu Arg Thr Asp Trp Ile Thr Arg Glu Gly Ala Gln Arg
85 90 95

Val Tyr Ile Glu Ile Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu Pro
100 105 110

Gly Val Met Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu
115 120 125

Ser Asp Asn Asp Lys Glu Arg Phe Ile Arg Glu Asn Gln Phe Val Lys
130 135 140

Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Val Asp Ile Gly
145 150 155 160

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Asp Arg Ile Met Lys Leu Asn Thr Glu Ile Arg Asp Val Gly Pro Leu
                165                 170                 175

Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Ile
            180                 185                 190

Ala Leu Val Ser Val Arg Val Phe Tyr Lys Lys Cys Pro Leu Thr Val
        195                 200                 205

Arg Asn Leu Ala Gln Phe Pro Asp Thr Ile Thr Gly Ala Asp Thr Ser
    210                 215                 220

Ser Leu Val Glu Val Arg Gly Ser Cys Val Asn Asn Ser Glu Glu Lys
225                 230                 235                 240

Asp Val Pro Lys Met Tyr Cys Gly Ala Asp Gly Glu Trp Leu Val Pro
                245                 250                 255

Ile Gly Asn Cys Leu Cys Asn Ala Gly His Glu Glu Arg Ser Gly Glu
            260                 265                 270

Cys Gln Ala Cys Lys Ile Gly Tyr Tyr Lys Ala Leu Ser Thr Asp Ala
        275                 280                 285

Thr Cys Ala Lys Cys Pro Pro His Ser Tyr Ser Val Trp Glu Gly Ala
    290                 295                 300

Thr Ser Cys Thr Cys Asp Arg Gly Phe Phe Arg Ala Asp Asn Asp Ala
305                 310                 315                 320

Ala Ser Met Pro Cys Thr Arg Pro Pro Ser Ala Pro Leu Asn Leu Ile
                325                 330                 335

Ser Asn Val Asn Glu Thr Ser Val Asn Leu Glu Trp Ser Ser Pro Gln
            340                 345                 350

Asn Thr Gly Gly Arg Gln Asp Ile Ser Tyr Asn Val Val Cys Lys Lys
        355                 360                 365

Cys Gly Ala Gly Asp Pro Ser Lys Cys Arg Pro Cys Gly Ser Gly Val
    370                 375                 380

His Tyr Thr Pro Gln Gln Asn Gly Leu Lys Thr Thr Lys Val Ser Ile
385                 390                 395                 400

Thr Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu Ile Trp Ala Val
                405                 410                 415

Asn Gly Val Ser Lys Tyr Asn Pro Asn Pro Asp Gln Ser Val Ser Val
            420                 425                 430

Thr Val Thr Thr Asn Gln Ala Ala Pro Ser Ser Ile Ala Leu Val Gln
        435                 440                 445

Ala Lys Glu Val Thr Arg Tyr Ser Val Ala Leu Ala Trp Leu Glu Pro
    450                 455                 460

Asp Arg Pro Asn Gly Val Ile Leu Glu Tyr Glu Val Lys Tyr Tyr Glu
465                 470                 475                 480

Lys Asp Gln Asn Glu Arg Ser Tyr Arg Ile Val Arg Thr Ala Ala Arg
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485 490 495

Asn Thr Asp Ile Lys Gly Leu Asn Pro Leu Thr Ser Tyr Val Phe His
500 505 510

Val Arg Ala Arg Thr Ala Ala Gly Tyr Gly Asp Phe Ser Glu Pro Leu
515 520 525

Glu Val Thr Thr Asn Thr Val Pro Ser Arg Ile Ile Gly Asp Gly Ala
530 535 540

Asn Ser Thr Val Leu Leu Val Ser Val Ser Gly Ser Val Val Leu Val
545 550 555 560

Val Ile Leu Ile Ala Ala Phe Val Ile Ser Arg Arg Arg Ser Lys Tyr
565 570 575

Ser Lys Ala Lys Gln Glu Ala Asp Glu Glu Lys His Leu Asn Gln Gly
580 585 590

Val Arg Thr Tyr Val Asp Pro Phe Thr Tyr Glu Asp Pro Asn Gln Ala
595 600 605

Val Arg Glu Phe Ala Lys Glu Ile Asp Ala Ser Cys Ile Lys Ile Glu
610 615 620

Lys Val Ile Gly Val Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu
625 630 635 640

Lys Val Pro Gly Lys Arg Glu Ile Cys Val Ala Ile Lys Thr Leu Lys
645 650 655

Ala Gly Tyr Thr Asp Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser
660 665 670

Ile Met Gly Gln Phe Asp His Pro Asn Ile Ile His Leu Glu Gly Val
675 680 685

Val Thr Lys Cys Lys Pro Val Met Ile Ile Thr Glu Tyr Met Glu Asn
690 695 700

Gly Ser Leu Asp Ala Phe Leu Arg Lys Asn Asp Gly Arg Phe Thr Val
705 710 715 720

Ile Gln Leu Val Gly Met Leu Arg Gly Ile Gly Ser Gly Met Lys Tyr
725 730 735

Leu Ser Asp Met Ser Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
740 745 750

Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Met Ser
755 760 765

Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly
770 775 780

Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Tyr Arg Lys
785 790 795 800

Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu
805 810 815

Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp
820 825 830

Pro Asn Thr Ala Leu Leu Asp Pro Ser Ser Pro Glu Phe Ser Ala Val
835 840 845

Val Ser Val Gly Asp Trp Leu Gln Ala Ile Lys Met Asp Arg Tyr Lys
850 855 860

Asp Asn Phe Thr Ala Ala Gly Tyr Thr Thr Leu Glu Ala Val Val His
865 870 875 880

Val Asn Gln Glu Asp Leu Ala Arg Ile Gly Ile Thr Ala Ile Thr His
885 890 895

Gln Asn Lys Ile Leu Ser Ser Val Gln Ala Met Arg Thr Gln Met Gln
900 905 910

Gln Met His Gly Arg Met Val Pro Val
915 920

<210> 53
<211> 444
<212> PRT
<213> Homo sapiens

<400> 53
Met Asn Asp Phe Gly Ile Lys Asn Met Asp Gln Val Ala Pro Val Ala
1 5 10 15

Asn Ser Tyr Arg Gly Thr Leu Lys Arg Gln Pro Ala Phe Asp Thr Phe
20 25 30

Asp Gly Ser Leu Phe Ala Val Phe Pro Ser Leu Asn Glu Glu Gln Thr
35 40 45

Leu Gln Glu Val Pro Thr Gly Leu Asp Ser Ile Ser His Asp Ser Ala
50 55 60

Asn Cys Glu Leu Pro Leu Leu Thr Pro Cys Ser Lys Ala Val Met Ser
65 70 75 80

Gln Ala Leu Lys Ala Thr Phe Ser Gly Phe Phe Trp Ala Thr Asn Glu
85 90 95

Phe Ser Leu Val Asn Val Asn Leu Gln Arg Phe Gly Met Asn Gly Gln
100 105 110

Met Leu Cys Asn Leu Gly Lys Glu Arg Phe Leu Glu Leu Ala Pro Asp
115 120 125

Phe Val Gly Asp Ile Leu Trp Glu His Leu Glu Gln Met Ile Lys Glu
130 135 140

Asn Gln Glu Lys Thr Glu Asp Gln Tyr Glu Glu Asn Ser His Leu Thr
145 150 155 160

Ser Val Pro His Trp Ile Asn Ser Asn Thr Leu Gly Phe Gly Thr Glu

165 170 175

Gln Ala Pro Tyr Gly Met Gln Thr Gln Asn Tyr Pro Lys Gly Gly Leu
180 185 190

Leu Asp Ser Met Cys Pro Ala Ser Thr Pro Ser Val Leu Ser Ser Glu
195 200 205

Gln Glu Phe Gln Met Phe Pro Lys Ser Arg Leu Ser Ser Val Ser Val
210 215 220

Thr Tyr Cys Ser Val Ser Gln Asp Phe Pro Gly Ser Asn Leu Asn Leu
225 230 235 240

Leu Thr Asn Asn Ser Gly Thr Pro Lys Asp His Asp Ser Pro Glu Asn
245 250 255

Gly Ala Asp Ser Phe Glu Ser Ser Asp Ser Leu Leu Gln Ser Trp Asn
260 265 270

Ser Gln Ser Ser Leu Leu Asp Val Gln Arg Val Pro Ser Phe Glu Ser
275 280 285

Phe Glu Asp Asp Cys Ser Gln Ser Leu Cys Leu Asn Lys Pro Thr Met
290 295 300

Ser Phe Lys Asp Tyr Ile Gln Glu Arg Ser Asp Pro Val Glu Gln Gly
305 310 315 320

Lys Pro Val Ile Pro Ala Ala Val Leu Ala Gly Phe Thr Gly Ser Gly
325 330 335

Pro Ile Gln Leu Trp Gln Phe Leu Leu Glu Leu Leu Ser Asp Lys Ser
340 345 350

Cys Gln Ser Phe Ile Ser Trp Thr Gly Asp Gly Trp Glu Phe Lys Leu
355 360 365

Ala Asp Pro Asp Glu Val Ala Arg Arg Trp Gly Lys Arg Lys Asn Lys
370 375 380

Pro Lys Met Asn Tyr Glu Lys Leu Ser Arg Gly Leu Arg Tyr Tyr Tyr
385 390 395 400

Asp Lys Asn Ile Ile His Lys Thr Ser Gly Lys Arg Tyr Val Tyr Arg
405 410 415

Phe Val Cys Asp Leu Gln Asn Leu Leu Gly Phe Thr Pro Glu Glu Leu
420 425 430

His Ala Ile Leu Gly Val Gln Pro Asp Thr Glu Asp
435 440

<210> 54
<211> 260
<212> PRT
<213> Homo sapiens

<400> 54

Met Ala Gly Ser Ala Met Ser Ser Lys Phe Phe Leu Val Ala Leu Ala
1   5   10   15

Ile Phe Phe Ser Phe Ala Gln Val Val Ile Glu Ala Asn Ser Trp Trp
            20   25   30

Ser Leu Gly Met Asn Asn Pro Val Gln Met Ser Glu Val Tyr Ile Ile
        35   40   45

Gly Ala Gln Pro Leu Cys Ser Gln Leu Ala Gly Leu Ser Gln Gly Gln
    50   55   60

Lys Lys Leu Cys His Leu Tyr Gln Asp His Met Gln Tyr Ile Gly Glu
65   70   75   80

Gly Ala Lys Thr Gly Ile Lys Glu Cys Gln Tyr Gln Phe Arg His Arg
                85   90   95

Arg Trp Asn Cys Ser Thr Val Asp Asn Thr Ser Val Phe Gly Arg Val
            100   105   110

Met Gln Ile Gly Ser Arg Glu Thr Ala Phe Thr Tyr Ala Val Ser Ala
        115   120   125

Ala Gly Val Val Asn Ala Met Ser Arg Ala Cys Arg Glu Gly Glu Leu
    130   135   140

Ser Thr Cys Gly Cys Ser Arg Ala Ala Arg Pro Lys Asp Leu Pro Arg
145   150   155   160

Asp Trp Leu Trp Gly Gly Cys Gly Asp Asn Ile Asp Tyr Gly Tyr Arg
                165   170   175

Phe Ala Lys Glu Phe Val Asp Ala Arg Glu Arg Glu Arg Ile His Ala
            180   185   190

Lys Gly Ser Tyr Glu Ser Ala Arg Ile Leu Met Asn Leu His Asn Asn
        195   200   205

Glu Ala Gly Arg Arg Thr Val Tyr Asn Leu Ala Asp Val Ala Cys Lys
    210   215   220

Cys His Gly Val Ser Gly Ser Cys Ser Leu Lys Thr Cys Trp Leu Gln
225   230   235   240

Leu Ala Asp Phe Arg Lys Val Gly Asp Ala Leu Lys Glu Lys Tyr Asp
                245   250   255

Thr Leu Val Gly
            260

<210> 55
<211> 719
<212> PRT
<213> Homo sapiens

<400> 55
Met Ala Leu Arg Arg Ser Met Gly Arg Pro Gly Leu Pro Pro Leu Pro
1   5   10   15

Leu Pro Pro Pro Pro Arg Leu Gly Leu Leu Leu Ala Glu Ser Ala Ala
20 25 30

Ala Gly Leu Lys Leu Met Gly Ala Pro Val Lys Leu Thr Val Ser Gln
35 40 45

Gly Gln Pro Val Lys Leu Asn Cys Ser Val Glu Gly Met Glu Glu Pro
50 55 60

Asp Ile Gln Trp Val Lys Asp Gly Ala Val Val Gln Asn Leu Asp Gln
65 70 75 80

Leu Tyr Ile Pro Val Ser Glu Gln His Trp Ile Gly Phe Leu Ser Leu
85 90 95

Lys Ser Val Glu Arg Ser Asp Ala Gly Arg Tyr Trp Cys Gln Val Glu
100 105 110

Asp Gly Gly Glu Thr Glu Ile Ser Gln Pro Val Trp Leu Thr Val Glu
115 120 125

Gly Val Pro Phe Phe Thr Val Glu Pro Lys Asp Leu Ala Val Pro Pro
130 135 140

Asn Ala Pro Phe Gln Leu Ser Cys Glu Ala Val Gly Pro Pro Glu Pro
145 150 155 160

Val Thr Ile Val Trp Trp Arg Gly Thr Thr Lys Ile Gly Gly Pro Ala
165 170 175

Pro Ser Pro Ser Val Leu Asn Val Thr Gly Val Thr Gln Ser Thr Met
180 185 190

Phe Ser Cys Glu Ala His Asn Leu Lys Gly Leu Ala Ser Ser Arg Thr
195 200 205

Ala Thr Val His Leu Gln Ala Leu Pro Ala Ala Pro Phe Asn Ile Thr
210 215 220

Val Thr Lys Leu Ser Ser Ser Asn Ala Ser Val Ala Trp Met Pro Gly
225 230 235 240

Ala Asp Gly Arg Ala Leu Leu Gln Ser Cys Thr Val Gln Val Thr Gln
245 250 255

Ala Pro Gly Gly Trp Glu Val Leu Ala Val Val Val Pro Val Pro Pro
260 265 270

Phe Thr Cys Leu Leu Arg Asp Leu Val Pro Ala Thr Asn Tyr Ser Leu
275 280 285

Arg Val Arg Cys Ala Asn Ala Leu Gly Pro Ser Pro Tyr Ala Asp Trp
290 295 300

Val Pro Phe Gln Thr Lys Gly Leu Ala Pro Ala Ser Ala Pro Gln Asn
305 310 315 320

Leu His Ala Ile Arg Thr Asp Ser Gly Leu Ile Leu Glu Trp Glu Glu
325 330 335

Val Ile Pro Glu Ala Pro Leu Glu Gly Pro Leu Gly Pro Tyr Lys Leu
340 345 350

Ser Trp Val Gln Asp Asn Gly Thr Gln Asp Glu Leu Thr Val Glu Gly
355 360 365

Thr Arg Ala Asn Leu Thr Gly Trp Asp Pro Gln Lys Asp Leu Ile Val
370 375 380

Arg Val Cys Val Ser Asn Ala Val Gly Cys Gly Pro Trp Ser Gln Pro
385 390 395 400

Leu Val Val Ser Ser His Asp Arg Ala Gly Gln Gln Gly Pro Pro His
405 410 415

Ser Arg Thr Ser Trp Val Pro Val Val Leu Gly Val Leu Thr Ala Leu
420 425 430

Val Thr Ala Ala Ala Leu Ala Leu Ile Leu Leu Arg Lys Arg Arg Lys
435 440 445

Glu Thr Arg Phe Gly Gln Ala Phe Asp Ser Val Met Ala Arg Gly Glu
450 455 460

Pro Ala Val His Phe Arg Ala Ala Arg Ser Phe Asn Arg Glu Arg Pro
465 470 475 480

Glu Arg Ile Glu Ala Thr Leu Asp Ser Leu Gly Ile Ser Asp Glu Leu
485 490 495

Lys Glu Lys Leu Glu Asp Val Leu Ile Pro Glu Gln Gln Phe Thr Leu
500 505 510

Gly Arg Met Leu Gly Lys Gly Glu Phe Gly Ser Val Arg Glu Ala Gln
515 520 525

Leu Lys Gln Glu Asp Gly Ser Phe Val Lys Val Ala Val Lys Met Leu
530 535 540

Lys Ala Asp Ile Ile Ala Ser Ser Asp Ile Glu Glu Phe Leu Arg Glu
545 550 555 560

Ala Ala Cys Met Lys Glu Phe Asp His Pro His Val Ala Lys Leu Val
565 570 575

Gly Val Ser Leu Arg Ser Arg Ala Lys Gly Arg Leu Pro Ile Pro Met
580 585 590

Val Ile Leu Pro Phe Met Lys His Gly Asp Leu His Ala Phe Leu Leu
595 600 605

Ala Ser Arg Ile Gly Glu Asn Pro Phe Asn Leu Pro Leu Gln Thr Leu
610 615 620

Ile Arg Phe Met Val Asp Ile Ala Cys Gly Met Glu Tyr Leu Ser Ser
625 630 635 640

Arg Asn Phe Ile His Arg Asp Leu Ala Ala Arg Asn Cys Met Leu Ala
645 650 655

Glu Asp Met Thr Val Cys Val Ala Asp Phe Gly Leu Ser Arg Lys Ile

660 665 670

Tyr Ser Asp Cys Arg Tyr Ile Leu Thr Pro Gly Gly Leu Ala Glu Gln
675 680 685

Pro Gly Gln Ala Glu His Gln Pro Glu Ser Pro Leu Asn Glu Thr Gln
690 695 700

Arg Leu Leu Leu Leu Gln Gln Gly Leu Leu Pro His Ser Ser Cys
705 710 715

<210> 56
<211> 848
<212> PRT
<213> Homo sapiens

<400> 56
Met Cys Arg Ile Ala Gly Ala Leu Arg Thr Leu Leu Pro Leu Leu Ala
1 5 10 15

Ala Leu Leu Gln Ala Ser Val Glu Ala Ser Gly Glu Ile Ala Leu Cys
20 25 30

Lys Thr Gly Phe Pro Glu Asp Val Tyr Ser Ala Val Leu Ser Lys Asp
35 40 45

Val His Glu Gly Gln Pro Leu Leu Asn Val Lys Phe Ser Asn Cys Asn
50 55 60

Gly Lys Arg Lys Val Gln Tyr Glu Ser Ser Glu Pro Ala Asp Phe Lys
65 70 75 80

Val Asp Glu Asp Gly Met Val Tyr Ala Val Arg Ser Phe Pro Leu Ser
85 90 95

Ser Glu His Ala Lys Phe Leu Ile Tyr Ala Gln Asp Lys Glu Thr Gln
100 105 110

Glu Lys Trp Gln Val Ala Val Lys Leu Ser Leu Lys Pro Thr Leu Thr
115 120 125

Glu Glu Ser Val Lys Glu Ser Ala Glu Val Glu Glu Ile Val Phe Pro
130 135 140

Arg Gln Phe Ser Lys His Ser Gly His Leu Gln Arg Gln Lys Arg Asp
145 150 155 160

Trp Val Ile Pro Pro Ile Asn Leu Pro Glu Asn Ser Arg Gly Pro Phe
165 170 175

Pro Gln Glu Leu Val Arg Ile Arg Ser Asp Arg Asp Lys Asn Leu Ser
180 185 190

Leu Arg Tyr Ser Val Thr Gly Pro Gly Ala Asp Gln Pro Pro Thr Gly
195 200 205

Ile Phe Ile Ile Asn Pro Ile Ser Gly Gln Leu Ser Val Thr Lys Pro
210 215 220

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Leu Asp Arg Glu Gln Ile Ala Arg Phe His Leu Arg Ala His Ala Val
225                 230                 235                 240

Asp Ile Asn Gly Asn Gln Val Glu Asn Pro Ile Asp Ile Val Ile Asn
                245                 250                 255

Val Ile Asp Met Asn Asp Asn Arg Pro Glu Phe Leu His Gln Val Trp
            260                 265                 270

Asn Gly Thr Val Pro Glu Gly Ser Lys Pro Gly Thr Tyr Val Met Thr
        275                 280                 285

Val Thr Ala Ile Asp Ala Asp Asp Pro Asn Ala Leu Asn Gly Met Leu
    290                 295                 300

Arg Tyr Arg Ile Val Ser Gln Ala Pro Ser Thr Pro Ser Pro Asn Met
305                 310                 315                 320

Phe Thr Ile Asn Asn Glu Thr Gly Asp Ile Ile Thr Val Ala Ala Gly
                325                 330                 335

Leu Asp Arg Glu Lys Val Gln Gln Tyr Thr Leu Ile Ile Gln Ala Thr
            340                 345                 350

Asp Met Glu Gly Asn Pro Thr Tyr Gly Leu Ser Asn Thr Ala Thr Ala
        355                 360                 365

Val Ile Thr Val Thr Asp Val Asn Asp Asn Pro Pro Glu Phe Thr Ala
    370                 375                 380

Met Thr Phe Tyr Gly Glu Val Pro Glu Asn Arg Val Asp Ile Ile Val
385                 390                 395                 400

Ala Asn Leu Thr Val Thr Asp Lys Asp Gln Pro His Thr Pro Ala Trp
                405                 410                 415

Asn Ala Val Tyr Arg Ile Ser Gly Gly Asp Pro Thr Gly Arg Phe Ala
            420                 425                 430

Ile Gln Thr Asp Pro Asn Ser Asn Asp Gly Leu Val Thr Val Val Lys
        435                 440                 445

Pro Ile Asp Phe Glu Thr Asn Arg Met Phe Val Leu Thr Val Ala Ala
    450                 455                 460

Glu Asn Gln Val Pro Leu Ala Lys Gly Ile Gln His Pro Pro Gln Ser
465                 470                 475                 480

Thr Ala Thr Val Ser Val Thr Val Ile Asp Val Asn Glu Asn Pro Tyr
                485                 490                 495

Phe Ala Pro Asn Pro Lys Ile Ile Arg Gln Glu Glu Gly Leu His Ala
            500                 505                 510

Gly Thr Met Leu Thr Thr Phe Thr Ala Gln Asp Pro Asp Arg Tyr Met
        515                 520                 525

Gln Gln Asn Ile Arg Tyr Thr Lys Leu Ser Asp Pro Ala Asn Trp Leu
    530                 535                 540

Lys Ile Asp Pro Val Asn Gly Gln Ile Thr Thr Ile Ala Val Leu Asp
```

545 550 555 560

Arg Glu Ser Pro Asn Val Lys Asn Asn Ile Tyr Asn Ala Thr Phe Leu
565 570 575

Ala Ser Asp Asn Gly Ile Pro Pro Met Ser Gly Thr Gly Thr Leu Gln
580 585 590

Ile Tyr Leu Leu Asp Ile Asn Asp Asn Ala Pro Gln Val Leu Pro Gln
595 600 605

Glu Ala Glu Thr Cys Glu Thr Pro Asp Pro Asn Ser Ile Asn Ile Thr
610 615 620

Ala Leu Asp Tyr Asp Ile Asp Pro Asn Ala Gly Pro Phe Ala Phe Asp
625 630 635 640

Leu Pro Leu Ser Pro Val Thr Ile Lys Arg Asn Trp Thr Ile Thr Arg
645 650 655

Leu Asn Gly Asp Phe Ala Gln Leu Asn Leu Lys Ile Lys Phe Leu Glu
660 665 670

Ala Gly Ile Tyr Glu Val Pro Ile Ile Ile Thr Asp Ser Gly Asn Pro
675 680 685

Pro Lys Ser Asn Ile Ser Ile Leu Arg Val Lys Val Cys Gln Cys Asp
690 695 700

Ser Asn Gly Asp Cys Thr Asp Val Asp Arg Ile Val Gly Ala Gly Leu
705 710 715 720

Gly Thr Gly Ala Ile Ile Ala Ile Leu Leu Cys Ile Ile Ile Leu Leu
725 730 735

Ile Leu Val Leu Met Phe Val Val Trp Met Lys Arg Arg Asp Lys Glu
740 745 750

Arg Gln Ala Lys Gln Leu Leu Ile Asp Pro Glu Asp Asp Val Arg Asp
755 760 765

Asn Ile Leu Lys Tyr Asp Glu Glu Gly Gly Gly Glu Glu Asp Gln Asp
770 775 780

Tyr Asp Leu Ser Gln Leu Gln Gln Pro Asp Thr Val Glu Pro Asp Ala
785 790 795 800

Ile Lys Pro Val Gly Ile Arg Arg Met Asp Glu Arg Pro Ile His Ala
805 810 815

Glu Pro Gln Tyr Pro Val Arg Ser Ala Ala Pro His Pro Gly Asp Ile
820 825 830

Gly Asp Phe Ile Asn Glu Lys Thr Trp Pro Ile Gln Ser Leu His Leu
835 840 845

<210> 57
<211> 103
<212> PRT
<213> Homo sapiens

<400> 57
Met Glu Arg Val Lys Met Ile Asn Val Gln Arg Leu Leu Glu Ala Ala
1 5 10 15

Glu Phe Leu Glu Arg Arg Glu Arg Glu Cys Glu His Gly Tyr Ala Ser
20 25 30

Ser Phe Pro Ser Met Pro Ser Pro Arg Leu Gln His Ser Lys Pro Pro
35 40 45

Arg Arg Leu Ser Arg Ala Gln Lys His Ser Ser Gly Ser Ser Asn Thr
50 55 60

Ser Thr Ala Asn Arg Ser Thr His Asn Glu Leu Glu Lys Asn Arg Leu
65 70 75 80

Lys Asn Trp Leu Val Gly Arg Arg Asp Thr Arg Gly Met Lys Met Leu
85 90 95

Leu Lys Ala Ile Ala Val Ile
100

<210> 58
<211> 234
<212> PRT
<213> Homo sapiens

<400> 58
Met Glu Lys His Ile Asn Thr Phe Leu Gln Asn Val Gln Ile Leu Leu
1 5 10 15

Glu Ala Ala Ser Tyr Leu Glu Gln Ile Glu Lys Glu Asn Lys Lys Cys
20 25 30

Glu His Gly Tyr Ala Ser Ser Phe Pro Ser Met Pro Ser Pro Arg Leu
35 40 45

Gln His Ser Lys Pro Pro Arg Arg Leu Ser Arg Ala Gln Lys His Ser
50 55 60

Ser Gly Ser Ser Asn Thr Ser Thr Ala Asn Arg Ser Thr His Asn Glu
65 70 75 80

Leu Glu Lys Asn Arg Arg Ala His Leu Arg Leu Cys Leu Glu Arg Leu
85 90 95

Lys Val Leu Ile Pro Leu Gly Pro Asp Cys Thr Arg His Thr Thr Leu
100 105 110

Gly Leu Leu Asn Lys Ala Lys Ala His Ile Lys Lys Leu Glu Glu Ala
115 120 125

Glu Arg Lys Ser Gln His Gln Leu Glu Asn Leu Glu Arg Glu Gln Arg
130 135 140

Phe Leu Lys Trp Arg Leu Glu Gln Leu Gln Gly Pro Gln Glu Met Glu
145 150 155 160

Arg Ile Arg Met Asp Ser Ile Gly Ser Thr Ile Ser Ser Asp Arg Ser
165 170 175

Asp Ser Glu Arg Glu Glu Ile Glu Val Asp Val Glu Ser Thr Glu Phe
180 185 190

Ser His Gly Glu Val Asp Asn Ile Ser Thr Thr Ser Ile Ser Asp Ile
195 200 205

Asp Asp His Ser Ser Leu Pro Ser Ile Gly Ser Asp Glu Gly Tyr Ser
210 215 220

Ser Ala Ser Val Lys Leu Ser Phe Thr Ser
225 230

<210> 59
<211> 329
<212> PRT
<213> Homo sapiens

<400> 59
Met Glu Ser Pro Ala Ser Ser Gln Pro Ala Ser Met Pro Gln Ser Lys
1 5 10 15

Gly Lys Ser Lys Arg Lys Lys Asp Leu Arg Ile Ser Cys Met Ser Lys
20 25 30

Pro Pro Ala Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp Ser Arg Thr
35 40 45

Phe Ile Thr Ile Gly Asp Arg Asn Phe Glu Val Glu Ala Asp Asp Leu
50 55 60

Val Thr Ile Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val Val Glu Lys
65 70 75 80

Val Arg His Ala Gln Ser Gly Thr Ile Met Ala Val Lys Arg Ile Arg
85 90 95

Ala Thr Val Asn Ser Gln Glu Gln Lys Arg Leu Leu Met Asp Leu Asp
100 105 110

Ile Asn Met Arg Thr Val Asp Cys Phe Tyr Thr Val Thr Phe Tyr Gly
115 120 125

Ala Leu Phe Arg Glu Gly Asp Val Trp Ile Cys Met Glu Leu Met Asp
130 135 140

Thr Ser Leu Asp Lys Phe Tyr Arg Lys Val Leu Asp Lys Asn Met Thr
145 150 155 160

Ile Pro Glu Asp Ile Leu Gly Glu Ile Ala Val Ser Ile Val Arg Ala
165 170 175

Leu Glu His Leu His Ser Lys Leu Ser Val Ile His Arg Asp Val Lys

180 185 190

Pro Ser Asn Val Leu Ile Asn Lys Glu Gly His Val Lys Met Cys Asp
195 200 205

Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser Val Ala Lys Thr Met Asp
210 215 220

Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu Arg Ile Asn Pro Glu Leu
225 230 235 240

Asn Gln Lys Gly Tyr Asn Val Lys Ser Asp Val Trp Ser Leu Gly Ile
245 250 255

Thr Met Ile Glu Met Ala Ile Leu Arg Phe Pro Tyr Glu Ser Trp Gly
260 265 270

Thr Pro Phe Gln Gln Leu Lys Gln Val Val Glu Glu Pro Ser Pro Gln
275 280 285

Leu Pro Ala Asp Arg Phe Ser Pro Glu Phe Val Asp Phe Thr Ala Gln
290 295 300

Cys Leu Arg Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu Glu Leu Ile
305 310 315 320

Gly Ala Asp Arg Phe Ser Pro Thr Pro
325

<210> 60
<211> 292
<212> PRT
<213> Homo sapiens

<400> 60
Met Pro Glu Ile Arg Leu Arg His Val Val Ser Cys Ser Ser Gln Asp
1 5 10 15

Ser Thr His Cys Ala Glu Asn Leu Leu Lys Ala Asp Thr Tyr Arg Lys
20 25 30

Trp Arg Ala Ala Lys Ala Gly Glu Lys Thr Ile Ser Val Val Leu Gln
35 40 45

Leu Glu Lys Glu Glu Gln Ile His Ser Val Asp Ile Gly Asn Asp Gly
50 55 60

Ser Ala Phe Val Glu Val Leu Val Gly Ser Ser Ala Gly Gly Ala Gly
65 70 75 80

Glu Gln Asp Tyr Glu Val Leu Leu Val Thr Ser Ser Phe Met Ser Pro
85 90 95

Ser Glu Ser Arg Ser Gly Ser Asn Pro Asn Arg Val Arg Met Phe Gly
100 105 110

Pro Asp Lys Leu Val Arg Ala Ala Ala Glu Lys Arg Trp Asp Arg Val
115 120 125

Lys Ile Val Cys Ser Gln Pro Tyr Ser Lys Asp Ser Pro Phe Gly Leu
    130   135   140

Ser Phe Val Arg Phe His Ser Pro Pro Asp Lys Asp Glu Ala Glu Ala
145   150   155   160

Pro Ser Gln Lys Val Thr Val Thr Lys Leu Gly Gln Phe Arg Val Lys
                165   170   175

Glu Glu Asp Glu Ser Ala Asn Ser Leu Arg Pro Gly Ala Leu Phe Phe
            180   185   190

Ser Arg Ile Asn Lys Thr Ser Pro Val Thr Ala Ser Asp Pro Ala Gly
        195   200   205

Pro Ser Tyr Ala Ala Ala Thr Leu Gln Ala Ser Ser Ala Ala Ser Ser
    210   215   220

Ala Ser Pro Val Ser Arg Ala Ile Gly Ser Thr Ser Lys Pro Gln Glu
225   230   235   240

Ser Pro Trp His Ser Phe Val Pro Asp Gly Ser Thr Val Ala Met Arg
                245   250   255

Ser Arg Ser Tyr Phe Leu Thr Ser Ser Met Gly Trp Cys Arg Lys Pro
            260   265   270

Glu Val Cys Ala Ile His Thr His Thr His Thr His Thr His Thr His
        275   280   285

Thr Arg Cys Ile
    290

<210> 61
<211> 266
<212> PRT
<213> Homo sapiens

<400> 61
Met Pro Glu Ile Arg Leu Arg His Val Val Ser Cys Ser Ser Gln Asp
1   5   10   15

Ser Thr His Cys Ala Glu Asn Leu Leu Lys Ala Asp Thr Tyr Arg Lys
            20   25   30

Trp Arg Ala Ala Lys Ala Gly Glu Lys Thr Ile Ser Val Val Leu Gln
        35   40   45

Leu Glu Lys Glu Glu Gln Ile His Ser Val Asp Ile Gly Asn Asp Gly
    50   55   60

Ser Ala Phe Val Glu Val Leu Val Gly Ser Ser Ala Gly Gly Ala Gly
65   70   75   80

Glu Gln Asp Tyr Glu Val Leu Leu Val Thr Ser Ser Phe Met Ser Pro
                85   90   95

Ser Glu Ser Arg Ser Gly Ser Asn Pro Asn Arg Val Arg Met Phe Gly
            100   105   110

Pro Asp Lys Leu Val Arg Ala Ala Ala Glu Lys Arg Trp Asp Arg Val
115 120 125

Lys Ile Val Cys Ser Gln Pro Tyr Ser Lys Asp Ser Pro Phe Gly Leu
130 135 140

Ser Phe Val Arg Phe His Ser Pro Pro Asp Lys Asp Glu Ala Glu Ala
145 150 155 160

Pro Ser Gln Lys Val Thr Val Thr Lys Leu Gly Gln Phe Arg Val Lys
165 170 175

Glu Glu Asp Glu Ser Ala Asn Ser Leu Arg Pro Gly Ala Leu Phe Phe
180 185 190

Ser Arg Ile Asn Lys Thr Ser Pro Val Thr Ala Ser Asp Pro Ala Gly
195 200 205

Pro Ser Tyr Ala Ala Ala Thr Leu Gln Ala Ser Ser Ala Ala Ser Ser
210 215 220

Ala Ser Pro Val Ser Arg Ala Ile Gly Ser Thr Ser Lys Pro Gln Glu
225 230 235 240

Ser Ser Asp Phe Gly Gly Val Glu Glu Glu Arg Ser Trp Arg Pro Gln
245 250 255

Ser Ile Pro Ile Pro Ser Ala Pro Gly Ser
260 265

<210> 62
<211> 247
<212> PRT
<213> Homo sapiens

<400> 62
Met Pro Glu Ile Arg Leu Arg His Val Val Ser Cys Ser Ser Gln Asp
1 5 10 15

Ser Thr His Cys Ala Glu Asn Leu Leu Lys Ala Asp Thr Tyr Arg Lys
20 25 30

Trp Arg Ala Ala Lys Ala Gly Glu Lys Thr Ile Ser Val Val Leu Gln
35 40 45

Leu Glu Lys Glu Glu Gln Ile His Ser Val Asp Ile Gly Asn Asp Gly
50 55 60

Ser Ala Phe Val Glu Val Leu Val Gly Ser Ser Ala Gly Gly Ala Gly
65 70 75 80

Glu Gln Asp Tyr Glu Val Leu Leu Val Thr Ser Ser Phe Met Ser Pro
85 90 95

Ser Glu Ser Arg Ser Gly Ser Asn Pro Asn Arg Val Arg Met Phe Gly
100 105 110

Pro Asp Lys Leu Val Arg Ala Ala Ala Glu Lys Arg Trp Asp Arg Val

115 120 125

Lys Ile Val Cys Ser Gln Pro Tyr Ser Lys Asp Ser Pro Phe Gly Leu
130 135 140

Ser Phe Val Arg Phe His Ser Pro Pro Asp Lys Asp Glu Ala Glu Ala
145 150 155 160

Pro Ser Gln Lys Val Thr Val Thr Lys Leu Gly Gln Phe Arg Val Lys
165 170 175

Glu Glu Asp Glu Ser Ala Asn Ser Leu Arg Leu Glu Asp Tyr Met Ser
180 185 190

Asp Arg Val Gln Phe Val Ile Thr Ala Gln Glu Trp Asp Pro Ser Phe
195 200 205

Glu Glu Ala Leu Met Asp Asn Pro Ser Leu Ala Phe Val Arg Pro Arg
210 215 220

Trp Ile Tyr Ser Cys Asn Glu Lys Gln Lys Leu Leu Pro His Gln Leu
225 230 235 240

Tyr Gly Val Val Pro Gln Ala
245

<210> 63
<211> 624
<212> PRT
<213> Homo sapiens

<400> 63
Met Pro Glu Ile Arg Leu Arg His Val Val Ser Cys Ser Ser Gln Asp
1 5 10 15

Ser Thr His Cys Ala Glu Asn Leu Leu Lys Ala Asp Thr Tyr Arg Lys
20 25 30

Trp Arg Ala Ala Lys Ala Gly Glu Lys Thr Ile Ser Val Val Leu Gln
35 40 45

Leu Glu Lys Glu Glu Gln Ile His Ser Val Asp Ile Gly Asn Asp Gly
50 55 60

Ser Ala Phe Val Glu Val Leu Val Gly Ser Ser Ala Gly Gly Ala Gly
65 70 75 80

Glu Gln Asp Tyr Glu Val Leu Leu Val Thr Ser Ser Phe Met Ser Pro
85 90 95

Ser Glu Ser Arg Ser Gly Ser Asn Pro Asn Arg Val Arg Met Phe Gly
100 105 110

Pro Asp Lys Leu Val Arg Ala Ala Ala Glu Lys Arg Trp Asp Arg Val
115 120 125

Lys Ile Val Cys Ser Gln Pro Tyr Ser Lys Asp Ser Pro Phe Gly Leu
130 135 140

Ser Phe Val Arg Phe His Ser Pro Pro Asp Lys Asp Glu Ala Glu Ala
145 150 155 160

Pro Ser Gln Lys Val Thr Val Thr Lys Leu Gly Gln Phe Arg Val Lys
165 170 175

Glu Glu Asp Glu Ser Ala Asn Ser Leu Arg Pro Gly Ala Leu Phe Phe
180 185 190

Ser Arg Ile Asn Lys Thr Ser Pro Val Thr Ala Ser Asp Pro Ala Gly
195 200 205

Pro Ser Tyr Ala Ala Ala Thr Leu Gln Ala Ser Ser Ala Ala Ser Ser
210 215 220

Ala Ser Pro Val Ser Arg Ala Ile Gly Ser Thr Ser Lys Pro Gln Glu
225 230 235 240

Ser Pro Lys Gly Lys Arg Lys Leu Asp Leu Asn Gln Glu Glu Lys Lys
245 250 255

Thr Pro Ser Lys Pro Pro Ala Gln Leu Ser Pro Ser Val Pro Lys Arg
260 265 270

Pro Lys Leu Pro Ala Pro Thr Arg Thr Pro Ala Thr Ala Pro Val Pro
275 280 285

Ala Arg Ala Gln Gly Ala Val Thr Gly Lys Pro Arg Gly Glu Gly Thr
290 295 300

Glu Pro Arg Arg Pro Arg Ala Gly Pro Glu Glu Leu Gly Lys Ile Leu
305 310 315 320

Gln Gly Val Val Val Val Leu Ser Gly Phe Gln Asn Pro Phe Arg Ser
325 330 335

Glu Leu Arg Asp Lys Ala Leu Glu Leu Gly Ala Lys Tyr Arg Pro Asp
340 345 350

Trp Thr Arg Asp Ser Thr His Leu Ile Cys Ala Phe Ala Asn Thr Pro
355 360 365

Lys Tyr Ser Gln Val Leu Gly Leu Gly Gly Arg Ile Val Arg Lys Glu
370 375 380

Trp Val Leu Asp Cys His Arg Met Arg Arg Arg Leu Pro Ser Arg Arg
385 390 395 400

Tyr Leu Met Ala Gly Pro Gly Ser Ser Ser Glu Glu Asp Glu Ala Ser
405 410 415

His Ser Gly Gly Ser Gly Asp Glu Ala Pro Lys Leu Pro Gln Lys Gln
420 425 430

Pro Gln Thr Lys Thr Lys Pro Thr Gln Ala Ala Gly Pro Ser Ser Pro
435 440 445

Gln Lys Pro Pro Thr Pro Glu Glu Thr Lys Ala Ala Ser Pro Val Leu
450 455 460

Gln Glu Asp Ile Asp Ile Glu Gly Val Gln Ser Glu Gly Gln Asp Asn

465 470 475 480

Gly Ala Glu Asp Ser Gly Asp Thr Glu Asp Glu Leu Arg Arg Val Ala
485 490 495

Glu Gln Lys Glu His Arg Leu Pro Pro Gly Gln Glu Glu Asn Gly Glu
500 505 510

Asp Pro Tyr Ala Gly Ser Thr Asp Glu Asn Thr Asp Ser Glu Glu His
515 520 525

Gln Glu Pro Pro Asp Leu Pro Val Pro Glu Leu Pro Arg Phe Leu Pro
530 535 540

Gly Gln Ala Leu Leu Ser Leu Arg Gly Val Pro Trp Gly Arg Ala Ala
545 550 555 560

Glu Thr His Pro Ile Arg His Ser Leu Gln Trp Gly Ala Pro Trp His
565 570 575

Ser Phe Val Pro Asp Gly Ser Thr Val Ala Met Arg Ser Arg Ser Tyr
580 585 590

Phe Leu Thr Ser Ser Met Gly Trp Cys Arg Lys Pro Glu Val Cys Ala
595 600 605

Ile His Thr His Thr His Thr His Thr His Thr His Thr Arg Cys Ile
610 615 620

<210> 64
<211> 567
<212> PRT
<213> Homo sapiens

<400> 64
Met Ala Gly Ala Ile Ala Ser Arg Met Ser Phe Ser Ser Leu Lys Arg
1 5 10 15

Lys Gln Pro Lys Thr Phe Thr Val Arg Ile Val Thr Met Asp Ala Glu
20 25 30

Met Glu Phe Asn Cys Glu Met Lys Trp Lys Gly Lys Asp Leu Phe Asp
35 40 45

Leu Val Cys Arg Thr Leu Gly Leu Arg Glu Thr Trp Phe Phe Gly Leu
50 55 60

Gln Tyr Thr Ile Lys Asp Thr Val Ala Trp Leu Lys Met Asp Lys Lys
65 70 75 80

Val Leu Asp His Asp Val Ser Lys Glu Glu Pro Val Thr Phe His Phe
85 90 95

Leu Ala Lys Phe Tyr Pro Glu Asn Ala Glu Glu Glu Leu Val Gln Glu
100 105 110

Ile Thr Gln His Leu Phe Phe Leu Gln Val Lys Lys Gln Ile Leu Asp
115 120 125

Glu Lys Ile Tyr Cys Pro Pro Glu Ala Ser Val Leu Leu Ala Ser Tyr
130 135 140

Ala Val Gln Ala Lys Tyr Gly Asp Tyr Asp Pro Ser Val His Lys Arg
145 150 155 160

Gly Phe Leu Ala Gln Glu Glu Leu Leu Pro Lys Arg Val Ile Asn Leu
165 170 175

Tyr Gln Met Thr Pro Glu Met Trp Glu Glu Arg Ile Thr Ala Trp Tyr
180 185 190

Ala Glu His Arg Gly Arg Ala Arg Asp Glu Ala Glu Met Glu Tyr Leu
195 200 205

Lys Ile Ala Gln Asp Leu Glu Met Tyr Gly Val Asn Tyr Phe Ala Ile
210 215 220

Arg Asn Lys Lys Gly Thr Glu Leu Leu Leu Gly Val Asp Ala Leu Gly
225 230 235 240

Leu His Ile Tyr Asp Pro Glu Asn Arg Leu Thr Pro Lys Ile Ser Phe
245 250 255

Pro Trp Lys Asn Glu Ile Arg Asn Ile Ser Tyr Ser Asp Lys Glu Phe
260 265 270

Thr Ile Lys Pro Leu Asp Lys Lys Ile Asp Val Phe Lys Phe Asn Ser
275 280 285

Ser Lys Leu Arg Val Asn Lys Leu Ile Leu Gln Leu Cys Ile Gly Asn
290 295 300

His Asp Leu Phe Met Arg Arg Arg Lys Ala Asp Ser Leu Glu Val Gln
305 310 315 320

Gln Met Lys Ala Gln Ala Arg Glu Glu Lys Ala Arg Lys Gln Met Lys
325 330 335

Glu Glu Ala Thr Met Ala Asn Glu Ala Leu Met Arg Ser Glu Glu Thr
340 345 350

Ala Asp Leu Leu Ala Glu Lys Ala Gln Ile Thr Glu Glu Glu Ala Lys
355 360 365

Leu Leu Ala Gln Lys Ala Ala Glu Ala Glu Gln Glu Met Gln Arg Ile
370 375 380

Lys Ala Thr Ala Ile Arg Thr Glu Glu Glu Lys Arg Leu Met Glu Gln
385 390 395 400

Lys Val Leu Glu Ala Glu Val Leu Ala Leu Lys Met Ala Glu Glu Ser
405 410 415

Glu Arg Arg Ala Lys Glu Ala Asp Gln Leu Lys Gln Asp Leu Gln Glu
420 425 430

Ala Arg Glu Ala Glu Arg Arg Ala Lys Gln Lys Leu Leu Glu Ile Ala

435 440 445

Thr Lys Pro Thr Tyr Pro Pro Met Asn Pro Ile Pro Ala Pro Leu Pro
450 455 460

Pro Asp Ile Pro Ser Phe Asn Leu Ile Gly Asp Ser Leu Ser Phe Asp
465 470 475 480

Phe Lys Asp Thr Asp Met Lys Arg Leu Ser Met Glu Ile Glu Lys Glu
485 490 495

Lys Val Glu Tyr Met Glu Lys Ser Lys His Leu Gln Glu Gln Leu Asn
500 505 510

Glu Leu Lys Thr Glu Ile Glu Ala Leu Lys Leu Lys Glu Arg Glu Thr
515 520 525

Ala Leu Asp Ile Leu His Asn Glu Asn Ser Asp Arg Gly Gly Ser Ser
530 535 540

Lys His Asn Thr Ile Lys Lys Leu Thr Leu Gln Ser Ala Lys Ser Arg
545 550 555 560

Val Ala Phe Phe Glu Glu Leu
565

<210> 65
<211> 134
<212> PRT
<213> Homo sapiens

<400> 65
Met Arg Glu Arg Phe Asp Arg Phe Leu His Glu Lys Asn Cys Met Thr
1 5 10 15

Asp Leu Leu Ala Lys Leu Glu Ala Lys Thr Gly Val Asn Arg Ser Phe
20 25 30

Ile Ala Leu Gly Val Ile Gly Leu Val Ala Leu Tyr Leu Val Phe Gly
35 40 45

Tyr Gly Ala Ser Leu Leu Cys Asn Leu Ile Gly Phe Gly Tyr Pro Ala
50 55 60

Tyr Ile Ser Ile Lys Ala Ile Glu Ser Pro Asn Lys Glu Asp Asp Thr
65 70 75 80

Gln Trp Leu Thr Tyr Trp Val Val Tyr Gly Val Phe Ser Ile Ala Glu
85 90 95

Phe Phe Ser Asp Ile Phe Leu Ser Trp Phe Pro Phe Tyr Tyr Met Leu
100 105 110

Lys Gln Ile Tyr Leu Glu Pro Pro Cys Ala Arg Phe Cys Ser Thr Ser
115 120 125

Gly Arg Tyr Phe Gly Glu
130

<210> 66
<211> 1278
<212> PRT
<213> Homo sapiens

<400> 66
Met Asp Leu Glu Gly Asp Arg Asn Gly Gly Ala Lys Lys Lys Asn Phe
1 5 10 15

Phe Lys Leu Asn Asn Lys Ser Glu Lys Asp Lys Lys Glu Lys Lys Pro
20 25 30

Thr Val Ser Val Phe Ser Met Phe Arg Tyr Ser Asn Trp Leu Asp Lys
35 40 45

Leu Tyr Met Val Val Gly Thr Leu Ala Ala Ile Ile His Gly Ala Gly
50 55 60

Leu Pro Leu Met Met Leu Val Phe Gly Glu Met Thr Asp Ile Phe Ala
65 70 75 80

Asn Ala Gly Asn Leu Glu Asp Leu Met Ser Asn Ile Thr Asn Arg Ser
85 90 95

Asp Ile Asn Asp Thr Gly Phe Phe Met Asn Leu Glu Glu Asp Met Thr
100 105 110

Arg Tyr Ala Tyr Tyr Tyr Ser Gly Ile Gly Ala Gly Val Leu Val Ala
115 120 125

Ala Tyr Ile Gln Val Ser Phe Trp Cys Leu Ala Ala Gly Arg Gln Ile
130 135 140

His Lys Ile Arg Lys Gln Phe Phe His Ala Ile Met Arg Gln Glu Ile
145 150 155 160

Gly Trp Phe Asp Val His Asp Val Gly Glu Leu Asn Thr Arg Leu Thr
165 170 175

Asp Asp Val Ser Lys Ile Asn Glu Val Ile Gly Asp Lys Ile Gly Met
180 185 190

Phe Phe Gln Ser Met Ala Thr Phe Phe Thr Gly Phe Ile Val Gly Phe
195 200 205

Thr Arg Gly Trp Lys Leu Thr Leu Val Ile Leu Ala Ile Ser Pro Val
210 215 220

Leu Gly Leu Ser Ala Ala Val Trp Ala Lys Ile Leu Ser Ser Phe Thr
225 230 235 240

Asp Lys Glu Leu Leu Ala Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu
245 250 255

Val Leu Ala Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln Lys Lys
260 265 270

Glu Leu Glu Arg Tyr Asn Lys Asn Leu Glu Glu Ala Lys Arg Ile Gly
275 280 285

Ile Lys Lys Ala Ile Thr Ala Asn Ile Ser Ile Gly Ala Ala Phe Leu
290 295 300

Leu Ile Tyr Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Thr Thr Leu
305 310 315 320

Val Leu Ser Gly Glu Tyr Ser Ile Gly Gln Val Leu Thr Val Phe Phe
325 330 335

Ser Val Leu Ile Gly Ala Phe Ser Val Gly Gln Ala Ser Pro Ser Ile
340 345 350

Glu Ala Phe Ala Asn Ala Arg Gly Ala Ala Tyr Glu Ile Phe Lys Ile
355 360 365

Ile Asp Asn Lys Pro Ser Ile Asp Ser Tyr Ser Lys Ser Gly His Lys
370 375 380

Pro Asp Asn Ile Lys Gly Asn Leu Glu Phe Arg Asn Val His Phe Ser
385 390 395 400

Tyr Pro Ser Arg Lys Glu Val Lys Ile Leu Lys Gly Leu Asn Leu Lys
405 410 415

Val Gln Ser Gly Gln Thr Val Ala Leu Val Gly Asn Ser Gly Cys Gly
420 425 430

Lys Ser Thr Thr Val Gln Leu Met Gln Arg Leu Tyr Asp Pro Thr Glu
435 440 445

Gly Met Val Ser Val Asp Gly Gln Asp Ile Arg Thr Ile Asn Val Arg
450 455 460

Phe Leu Arg Glu Ile Ile Gly Val Val Ser Gln Glu Pro Val Leu Phe
465 470 475 480

Ala Thr Thr Ile Ala Glu Asn Ile Arg Tyr Gly Arg Glu Asn Val Thr
485 490 495

Met Asp Glu Ile Glu Lys Ala Val Lys Glu Ala Asn Ala Tyr Asp Phe
500 505 510

Ile Met Lys Leu Pro His Lys Phe Asp Thr Leu Val Gly Glu Arg Gly
515 520 525

Ala Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala
530 535 540

Leu Val Arg Asn Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala
545 550 555 560

Leu Asp Thr Glu Ser Glu Ala Val Val Gln Val Ala Leu Asp Lys Ala
565 570 575

Arg Lys Gly Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser Thr Val
580 585 590

Arg Asn Ala Asp Val Ile Ala Gly Phe Asp Asp Gly Val Ile Val Glu
595 600 605

Lys Gly Asn His Asp Glu Leu Met Lys Glu Lys Gly Ile Tyr Phe Lys
610 615 620

Leu Val Thr Met Gln Thr Ala Gly Asn Glu Val Glu Leu Glu Asn Ala
625 630 635 640

Ala Asp Glu Ser Lys Ser Glu Ile Asp Ala Leu Glu Met Ser Ser Asn
645 650 655

Asp Ser Arg Ser Ser Leu Ile Arg Lys Arg Ser Thr Arg Arg Ser Val
660 665 670

Arg Gly Ser Gln Ala Gln Asp Arg Lys Leu Ser Thr Lys Glu Ala Leu
675 680 685

Asp Glu Ser Ile Pro Pro Val Ser Phe Trp Arg Ile Met Lys Leu Asn
690 695 700

Leu Thr Glu Trp Pro Tyr Phe Val Val Gly Val Phe Cys Ala Ile Ile
705 710 715 720

Asn Gly Gly Leu Gln Pro Ala Phe Ala Ile Ile Phe Ser Lys Ile Ile
725 730 735

Gly Val Phe Thr Arg Ile Asp Asp Pro Glu Thr Lys Arg Gln Asn Ser
740 745 750

Asn Leu Phe Ser Leu Leu Phe Leu Ala Leu Gly Ile Ile Ser Phe Ile
755 760 765

Thr Phe Phe Leu Gln Gly Phe Thr Phe Gly Lys Ala Gly Glu Ile Leu
770 775 780

Thr Lys Arg Leu Arg Tyr Met Val Phe Arg Ser Met Leu Arg Gln Asp
785 790 795 800

Val Ser Trp Phe Asp Asp Pro Lys Asn Thr Thr Gly Ala Leu Thr Thr
805 810 815

Arg Leu Ala Asn Asp Ala Ala Gln Val Lys Gly Ala Ile Gly Ser Arg
820 825 830

Leu Ala Val Ile Thr Gln Asn Ile Ala Asn Leu Gly Thr Gly Ile Ile
835 840 845

Ile Ser Phe Ile Tyr Gly Trp Gln Leu Thr Leu Leu Leu Leu Ala Ile
850 855 860

Val Pro Ile Ile Ala Ile Ala Gly Val Val Glu Met Lys Met Leu Ser
865 870 875 880

Gly Gln Ala Leu Lys Asp Lys Lys Glu Leu Glu Gly Ala Gly Lys Ile
885 890 895

Ala Thr Glu Ala Ile Glu Asn Phe Arg Thr Val Val Ser Leu Thr Gln
900 905 910

Glu Gln Lys Phe Glu His Met Tyr Ala Gln Ser Leu Gln Val Pro Tyr
915 920 925

Arg Asn Ser Leu Arg Lys Ala His Ile Phe Gly Ile Thr Phe Ser Phe

930 935 940

Thr Gln Ala Met Met Tyr Phe Ser Tyr Ala Gly Cys Phe Arg Phe Gly
945 950 955 960

Ala Tyr Leu Val Ala His Lys Leu Met Ser Phe Glu Asp Val Leu Leu
965 970 975

Val Phe Ser Ala Val Val Phe Gly Ala Met Ala Val Gly Gln Val Ser
980 985 990

Ser Phe Ala Pro Asp Tyr Ala Lys Ala Lys Ile Ser Ala Ala His Ile
995 1000 1005

Ile Met Ile Ile Glu Lys Thr Pro Leu Ile Asp Ser Tyr Ser Thr Glu
1010 1015 1020

Gly Leu Met Pro Asn Thr Leu Glu Gly Asn Val Thr Phe Gly Glu Val
1025 1030 1035 1040

Val Phe Asn Tyr Pro Thr Arg Pro Asp Ile Pro Val Leu Gln Gly Leu
1045 1050 1055

Ser Leu Glu Val Lys Lys Gly Gln Thr Leu Ala Leu Val Gly Ser Ser
1060 1065 1070

Gly Cys Gly Lys Ser Thr Val Val Gln Leu Leu Glu Arg Phe Tyr Asp
1075 1080 1085

Pro Leu Ala Gly Lys Val Leu Leu Asp Gly Lys Glu Ile Lys Arg Leu
1090 1095 1100

Asn Val Gln Trp Leu Arg Ala His Leu Gly Ile Val Ser Gln Glu Pro
1105 1110 1115 1120

Ile Leu Phe Asp Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly Asp Asn
1125 1130 1135

Ser Arg Val Val Ser Gln Glu Glu Ile Val Arg Ala Ala Lys Glu Ala
1140 1145 1150

Asn Ile His Ala Phe Ile Glu Ser Leu Pro Asn Lys Tyr Ser Thr Lys
1155 1160 1165

Val Gly Asp Lys Gly Thr Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile
1170 1175 1180

Ala Ile Ala Arg Ala Leu Val Arg Gln Pro His Ile Leu Leu Leu Asp
1185 1190 1195 1200

Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Lys Val Val Gln Glu
1205 1210 1215

Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Cys Ile Val Ile Ala His
1220 1225 1230

Arg Leu Ser Thr Ile Gln Asn Ala Asp Leu Ile Val Val Phe Gln Asn
1235 1240 1245

Gly Arg Val Lys Glu His Gly Thr His Gln Gln Leu Leu Ala Gln Lys
1250 1255 1260

Gly Ile Tyr Phe Ser Met Val Ser Val Gln Ala Gly Thr Ile
1265 1270 1275

<210> 67
<211> 579
<212> PRT
<213> Homo sapiens

<400> 67
Met Asp Leu Glu Gly Asp Arg Asn Gly Gly Ala Lys Lys Lys Asn Phe
1 5 10 15

Phe Lys Leu Asn Asn Lys Ser Glu Lys Asp Lys Lys Glu Lys Lys Pro
20 25 30

Thr Val Ser Val Phe Ser Met Phe Arg Tyr Ser Asn Trp Leu Asp Lys
35 40 45

Leu Tyr Met Val Val Gly Thr Leu Ala Ala Ile Ile His Gly Ala Gly
50 55 60

Leu Pro Leu Met Met Leu Val Phe Gly Glu Met Thr Asp Ile Phe Ala
65 70 75 80

Asn Ala Gly Asn Leu Glu Asp Leu Met Ser Asn Ile Thr Asn Arg Ser
85 90 95

Asp Ile Asn Asp Thr Gly Phe Phe Met Asn Leu Glu Glu Asp Met Thr
100 105 110

Arg Tyr Ala Tyr Tyr Tyr Ser Gly Ile Gly Ala Gly Val Leu Val Ala
115 120 125

Ala Tyr Ile Gln Val Ser Phe Trp Cys Leu Ala Ala Gly Arg Gln Ile
130 135 140

His Lys Ile Arg Lys Gln Phe Phe His Ala Ile Met Arg Gln Glu Ile
145 150 155 160

Gly Trp Phe Asp Val His Asp Val Gly Glu Leu Asn Thr Arg Leu Thr
165 170 175

Asp Asp Val Ser Lys Ile Asn Glu Gly Ile Gly Asp Lys Ile Gly Met
180 185 190

Phe Phe Gln Ser Met Ala Thr Phe Phe Thr Gly Phe Ile Val Gly Phe
195 200 205

Thr Arg Gly Trp Lys Leu Thr Leu Val Ile Leu Ala Ile Ser Pro Val
210 215 220

Leu Gly Leu Ser Ala Ala Val Trp Ala Lys Ile Leu Ser Ser Phe Thr
225 230 235 240

Asp Lys Glu Leu Leu Ala Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu
245 250 255

Val Leu Ala Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln Lys Lys

260 265 270

Glu Leu Glu Arg Tyr Asn Lys Asn Leu Glu Glu Ala Lys Arg Ile Gly
275 280 285

Ile Lys Lys Ala Ile Thr Ala Asn Ile Ser Ile Gly Ala Ala Phe Leu
290 295 300

Leu Ile Tyr Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Thr Thr Leu
305 310 315 320

Val Leu Ser Gly Glu Tyr Ser Ile Gly Gln Val Leu Thr Val Phe Phe
325 330 335

Ser Val Leu Ile Gly Ala Phe Ser Val Gly Gln Ala Ser Pro Ser Ile
340 345 350

Glu Ala Phe Ala Asn Ala Arg Gly Ala Ala Tyr Glu Ile Phe Lys Ile
355 360 365

Ile Asp Asn Lys Pro Ser Ile Asp Ser Tyr Ser Lys Ser Gly His Lys
370 375 380

Pro Asp Asn Ile Lys Gly Asn Leu Glu Phe Arg Asn Val His Phe Ser
385 390 395 400

Tyr Pro Ser Arg Lys Glu Val Lys Ile Leu Lys Gly Leu Asn Leu Lys
405 410 415

Val Gln Ser Gly Gln Thr Val Ala Leu Val Gly Asn Ser Gly Cys Gly
420 425 430

Lys Ser Thr Thr Val Gln Leu Met Gln Arg Leu Tyr Asp Pro Thr Glu
435 440 445

Gly Met Val Ser Val Asp Gly Gln Asp Ile Arg Thr Ile Asn Val Arg
450 455 460

Phe Leu Arg Glu Ile Ile Gly Val Val Ser Gln Glu Pro Val Leu Phe
465 470 475 480

Ala Thr Thr Ile Ala Glu Asn Ile Arg Tyr Gly Arg Glu Asn Val Thr
485 490 495

Met Asp Glu Ile Glu Lys Ala Val Lys Glu Ala Asn Ala Tyr Asp Phe
500 505 510

Ile Met Lys Leu Pro His Lys Phe Asp Thr Leu Val Gly Glu Arg Gly
515 520 525

Ala Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala
530 535 540

Leu Val Arg Asn Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala
545 550 555 560

Leu Asp Thr Glu Ser Glu Ala Glu Val Gln Ala Ala Leu Asp Lys Val
565 570 575

Ser Arg Leu

<210> 68
<211> 218
<212> PRT
<213> Homo sapiens

<400> 68
Met Ser Arg Ser Lys Arg Asp Asn Asn Phe Tyr Ser Val Glu Ile Gly
1 5 10 15

Asp Ser Thr Phe Thr Val Leu Lys Arg Tyr Gln Asn Leu Lys Pro Ile
20 25 30

Gly Ser Gly Ala Gln Gly Ile Val Cys Ala Ala Tyr Asp Ala Ile Leu
35 40 45

Glu Arg Asn Val Ala Ile Lys Lys Leu Ser Arg Pro Phe Gln Asn Gln
50 55 60

Thr His Ala Lys Arg Ala Tyr Arg Glu Leu Val Leu Met Lys Cys Val
65 70 75 80

Asn His Lys Asn Ile Ile Gly Leu Leu Asn Val Phe Thr Pro Gln Lys
85 90 95

Ser Leu Glu Glu Phe Gln Asp Val Tyr Ile Val Met Glu Leu Met Asp
100 105 110

Ala Asn Leu Cys Gln Val Ile Gln Met Glu Leu Asp His Glu Arg Met
115 120 125

Ser Tyr Leu Leu Tyr Gln Met Leu Cys Gly Ile Lys His Leu His Ser
130 135 140

Ala Gly Ile Ile His Arg Asp Leu Lys Pro Ser Asn Ile Val Val Lys
145 150 155 160

Ser Asp Cys Thr Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg Thr Ala
165 170 175

Gly Thr Ser Phe Met Met Thr Pro Tyr Val Val Thr Arg Tyr Tyr Arg
180 185 190

Ala Pro Glu Val Ile Leu Gly Met Gly Tyr Lys Glu Asn Gly Gly Arg
195 200 205

Met Gly Lys Gly Ile Phe Thr Arg Leu Gln
210 215

<210> 69
<211> 307
<212> PRT
<213> Homo sapiens

<400> 69
Met Ser Arg Ser Lys Arg Asp Asn Asn Phe Tyr Ser Val Glu Ile Gly
1 5 10 15

Asp Ser Thr Phe Thr Val Leu Lys Arg Tyr Gln Asn Leu Lys Pro Ile
20 25 30

Gly Ser Gly Ala Gln Gly Ile Val Cys Ala Ala Tyr Asp Ala Ile Leu
35 40 45

Glu Arg Asn Val Ala Ile Lys Lys Leu Ser Arg Pro Phe Gln Asn Gln
50 55 60

Thr His Ala Lys Arg Ala Tyr Arg Glu Leu Val Leu Met Lys Cys Val
65 70 75 80

Asn His Lys Asn Ile Ile Gly Leu Leu Asn Val Phe Thr Pro Gln Lys
85 90 95

Ser Leu Glu Glu Phe Gln Asp Val Tyr Ile Val Met Glu Leu Met Asp
100 105 110

Ala Asn Leu Cys Gln Val Ile Gln Met Glu Leu Asp His Glu Arg Met
115 120 125

Ser Tyr Leu Leu Tyr Gln Met Leu Cys Gly Ile Lys His Leu His Ser
130 135 140

Ala Gly Ile Ile His Arg Asp Leu Lys Pro Ser Asn Ile Val Val Lys
145 150 155 160

Ser Asp Cys Thr Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg Thr Ala
165 170 175

Gly Thr Ser Phe Met Met Thr Pro Tyr Val Val Thr Arg Tyr Tyr Arg
180 185 190

Ala Pro Glu Val Ile Leu Gly Met Gly Tyr Lys Glu Asn Val Asp Leu
195 200 205

Trp Ser Val Gly Cys Ile Met Gly Glu Met Val Cys His Lys Ile Leu
210 215 220

Phe Pro Gly Arg Asp Tyr Ile Asp Gln Trp Asn Lys Val Ile Glu Gln
225 230 235 240

Leu Gly Thr Pro Cys Pro Glu Phe Met Lys Lys Leu Gln Pro Thr Val
245 250 255

Arg Thr Tyr Val Glu Asn Arg Pro Lys Tyr Ala Gly Tyr Ser Phe Glu
260 265 270

Lys Leu Phe Pro Asp Val Leu Phe Pro Ala Asp Ser Glu His Asn Lys
275 280 285

Leu Lys Ala Ser Gln Tyr Phe Leu Gln Ile Cys Thr Phe Asn Pro Ile
290 295 300

Trp Gly Val
305

<210> 70

<211> 339
<212> PRT
<213> Homo sapiens

<400> 70

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Met Ser Arg Ser Lys Arg Asp Asn Asn Phe Tyr Ser Val Glu Ile Gly
1               5                   10                  15

Asp Ser Thr Phe Thr Val Leu Lys Arg Tyr Gln Asn Leu Lys Pro Ile
            20                  25                  30

Gly Ser Gly Ala Gln Gly Ile Val Cys Ala Ala Tyr Asp Ala Ile Leu
        35                  40                  45

Glu Arg Asn Val Ala Ile Lys Lys Leu Ser Arg Pro Phe Gln Asn Gln
    50                  55                  60

Thr His Ala Lys Arg Ala Tyr Arg Glu Leu Val Leu Met Lys Cys Val
65                  70                  75                  80

Asn His Lys Asn Ile Ile Gly Leu Leu Asn Val Phe Thr Pro Gln Lys
                85                  90                  95

Ser Leu Glu Glu Phe Gln Asp Val Tyr Ile Val Met Glu Leu Met Asp
            100                 105                 110

Ala Asn Leu Cys Gln Val Ile Gln Met Glu Leu Asp His Glu Arg Met
        115                 120                 125

Ser Tyr Leu Leu Tyr Gln Met Leu Cys Gly Ile Lys His Leu His Ser
    130                 135                 140

Ala Gly Ile Ile His Arg Asp Leu Lys Pro Ser Asn Ile Val Val Lys
145                 150                 155                 160

Ser Asp Cys Thr Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg Thr Ala
                165                 170                 175

Gly Thr Ser Phe Met Met Thr Pro Tyr Val Val Thr Arg Tyr Tyr Arg
            180                 185                 190

Ala Pro Glu Val Ile Leu Gly Met Gly Tyr Lys Glu Asn Val Asp Leu
        195                 200                 205

Trp Ser Val Gly Cys Ile Met Gly Glu Met Val Cys His Lys Ile Leu
    210                 215                 220

Phe Pro Gly Arg Asp Tyr Ile Asp Gln Trp Asn Lys Val Ile Glu Gln
225                 230                 235                 240

Leu Gly Thr Pro Cys Pro Glu Phe Met Lys Lys Leu Gln Pro Thr Val
                245                 250                 255

Arg Thr Tyr Val Glu Asn Arg Pro Lys Tyr Ala Gly Tyr Ser Phe Glu
            260                 265                 270

Lys Leu Phe Pro Asp Val Leu Phe Pro Ala Asp Ser Glu His Asn Lys
        275                 280                 285

Leu Lys Ala Ser Gln Ala Arg Asp Leu Leu Ser Lys Met Leu Val Ile
    290                 295                 300
```

Asp Ala Ser Lys Arg Ile Ser Val Asp Glu Ala Leu Gln His Pro Tyr
305   310   315   320

Ile Asn Val Trp Tyr Asp Pro Ser Glu Ala Glu Ala Arg Ser Cys Lys
                325   330   335

Leu Phe Ser

<210> 71
<211> 178
<212> PRT
<213> Homo sapiens

<400> 71
Ala Arg Ser Gly Phe Tyr Arg Gln Glu Val Thr Lys Thr Ala Trp Glu
  1   5   10   15

Val Arg Ala Val Tyr Arg Asp Leu Gln Pro Val Gly Ser Gly Ala Tyr
            20   25   30

Gly Ala Val Cys Ser Ala Val Asp Gly Arg Thr Gly Ala Lys Val Ala
        35   40   45

Ile Lys Lys Leu Tyr Arg Pro Phe Gln Ser Glu Leu Phe Ala Lys Arg
    50   55   60

Ala Tyr Arg Glu Leu Arg Leu Leu Lys His Met Arg His Glu Asn Val
65   70   75   80

Ile Gly Leu Leu Asp Val Phe Thr Pro Asp Glu Thr Leu Asp Asp Phe
                85   90   95

Thr Asp Phe Tyr Leu Val Met Pro Phe Met Gly Thr Asp Leu Gly Lys
            100   105   110

Leu Met Lys His Glu Lys Leu Gly Glu Asp Arg Ile Gln Phe Leu Val
        115   120   125

Tyr Gln Met Leu Lys Gly Leu Arg Tyr Ile His Ala Ala Gly Ile Ile
    130   135   140

His Arg Val Ser Pro Gly Gly Glu Ala Ala His Gln Pro Ser Pro Ser
145   150   155   160

Ala Ile Pro Pro Pro Pro Arg Pro Thr Cys Glu Asp Val Met Gly Ser
                165   170   175

Gly Cys

<210> 72
<211> 648
<212> PRT
<213> Homo sapiens

<400> 72

Met Ser Pro Phe Leu Arg Ile Gly Leu Ser Asn Phe Asp Cys Gly Ser
1   5   10   15

Cys Gln Ser Cys Gln Gly Glu Ala Val Asn Pro Tyr Cys Ala Val Leu
            20   25   30

Val Lys Glu Tyr Val Glu Ser Glu Asn Gly Gln Met Tyr Ile Gln Lys
        35   40   45

Lys Pro Thr Met Tyr Pro Pro Trp Asp Ser Thr Phe Asp Ala His Ile
    50   55   60

Asn Lys Gly Arg Val Met Gln Ile Ile Val Lys Gly Lys Asn Val Asp
65   70   75   80

Leu Ile Ser Glu Thr Thr Val Glu Leu Tyr Ser Leu Ala Glu Arg Cys
                85   90   95

Arg Lys Asn Asn Gly Lys Thr Glu Ile Trp Leu Glu Leu Lys Pro Gln
            100   105   110

Gly Arg Met Leu Met Asn Ala Arg Tyr Phe Leu Glu Met Ser Asp Thr
        115   120   125

Lys Asp Met Asn Glu Phe Glu Thr Glu Gly Phe Phe Ala Leu His Gln
    130   135   140

Arg Arg Gly Ala Ile Lys Gln Ala Lys Val His His Val Lys Cys His
145   150   155   160

Glu Phe Thr Ala Thr Phe Phe Pro Gln Pro Thr Phe Cys Ser Val Cys
                165   170   175

His Glu Phe Val Trp Gly Leu Asn Lys Gln Gly Tyr Gln Cys Arg Gln
            180   185   190

Cys Asn Ala Ala Ile His Lys Lys Cys Ile Asp Lys Val Ile Ala Lys
        195   200   205

Cys Thr Gly Ser Ala Ile Asn Ser Arg Glu Thr Met Phe His Lys Glu
    210   215   220

Arg Phe Lys Ile Asp Met Pro His Arg Phe Lys Val Tyr Asn Tyr Lys
225   230   235   240

Ser Pro Thr Phe Cys Glu His Cys Gly Thr Leu Leu Trp Gly Leu Ala
                245   250   255

Arg Gln Gly Leu Lys Cys Asp Ala Cys Gly Met Asn Val His His Arg
            260   265   270

Cys Gln Thr Lys Val Ala Asn Leu Cys Gly Ile Asn Gln Lys Leu Met
        275   280   285

Ala Glu Ala Leu Ala Met Ile Glu Ser Thr Gln Gln Ala Arg Cys Leu
    290   295   300

Arg Asp Thr Glu Gln Ile Phe Arg Glu Gly Pro Val Glu Ile Gly Leu
305   310   315   320

Pro Cys Ser Ile Lys Asn Glu Ala Arg Pro Pro Cys Leu Pro Thr Pro
325 330 335

Gly Lys Arg Glu Pro Gln Gly Ile Ser Trp Glu Ser Pro Leu Asp Glu
340 345 350

Val Asp Lys Met Cys His Leu Pro Glu Pro Glu Leu Asn Lys Glu Arg
355 360 365

Pro Ser Leu Gln Ile Lys Leu Lys Ile Glu Asp Phe Ile Leu His Lys
370 375 380

Met Leu Gly Lys Gly Ser Phe Gly Lys Val Phe Leu Ala Glu Phe Lys
385 390 395 400

Lys Thr Asn Gln Phe Phe Ala Ile Lys Ala Leu Lys Lys Asp Val Val
405 410 415

Leu Met Asp Asp Asp Val Glu Cys Thr Met Val Glu Lys Arg Val Leu
420 425 430

Ser Leu Ala Trp Glu His Pro Phe Leu Thr His Met Phe Cys Thr Phe
435 440 445

Gln Thr Lys Glu Asn Leu Phe Phe Val Met Glu Tyr Leu Asn Gly Gly
450 455 460

Asp Leu Met Tyr His Ile Gln Ser Cys His Lys Phe Asp Leu Ser Arg
465 470 475 480

Ala Thr Phe Tyr Ala Ala Glu Ile Ile Leu Gly Leu Gln Phe Leu His
485 490 495

Ser Lys Gly Ile Val Tyr Arg Asp Leu Lys Leu Asp Asn Ile Leu Leu
500 505 510

Asp Lys Asp Gly His Ile Lys Ile Ala Asp Phe Gly Met Cys Lys Glu
515 520 525

Asn Met Leu Gly Asp Ala Lys Thr Asn Thr Phe Cys Gly Thr Pro Asp
530 535 540

Tyr Ile Ala Pro Glu Ile Leu Leu Gly Gln Lys Tyr Asn His Ser Val
545 550 555 560

Asp Trp Trp Ser Phe Gly Val Leu Leu Tyr Glu Met Leu Ile Gly Gln
565 570 575

Ser Pro Phe His Gly Gln Asp Glu Glu Glu Leu Phe His Ser Ile Arg
580 585 590

Met Asp Asn Pro Phe Tyr Pro Arg Trp Leu Glu Lys Glu Ala Lys Asp
595 600 605

Leu Leu Val Lys Val Arg Ser Glu Ala Lys Ser Val Phe Ile Arg Arg
610 615 620

Ala Leu Gly Leu Leu Val Ser Phe Leu Phe Leu Leu Val Ser Asn Leu
625 630 635 640

His Val Ala Asn Asn Asp Tyr Tyr

645

```
  1 MVRSGNKAAVVLCMDVGFTMSNSIPGIESPFEQAKKVITMFVQRQVFAEN  50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MVRSGNKAAVVLCMDVGFTMSNSIPGIESPFEQAKKVITMFVQRQVFAEN  50
             .         .         .         .         .
 51 KDEIALVLFGTDGTDNPLSGGDQYQNITVHRHLMLPDFDLLEDIESKIQP 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 KDEIALVLFGTDGTDNPLSGGDQYQNITVHRHLMLPDFDLLEDIESKIQP 100
             .         .         .         .         .
101 GSQQADFLDALIVSMDVIQHETIGKKFEKRHIEIFTDLSSRFSKSQLDII 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 GSQQADFLDALIVSMDVIQHETIGKKFEKRHIEIFTDLSSRFSKSQLDII 150
             .         .         .         .         .
151 IHSLKKCDISLQFFLPFSLGKEDGSGDRGDGPFRLGGHGPSFPLKGITEQ 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 IHSLKKCDISLQFFLPFSLGKEDGSGDRGDGPFRLGGHGPSFPLKGITEQ 200
             .         .         .         .         .
201 QKEGLEIVKMVMISLEGEDGLDEIYSFSESLRKLCVFKKIERHSIHWPCR 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 QKEGLEIVKMVMISLEGEDGLDEIYSFSESLRKLCVFKKIERHSIHWPCR 250
```

Fig. 1

```
                 .         .         .         .         .
251 LTIGSNLSIRIAAYKSILQERVKKTWTVVDAKTLKKEDIQKETVYCLNDD 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 LTIGSNLSIRIAAYKSILQERVKKTWTVVDAKTLKKEDIQKETVYCLNDD 300
                 .         .         .         .         .
301 DETEVLKEDIIQGFRYGSDIVPFSKVDEEQMKYKSEGKCFSVLGFCKSSQ 350
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 DETEVLKEDIIQGFRYGSDIVPFSKVDEEQMKYKSEGKCFSVLGFCKSSQ 350
                 .         .         .         .         .
351 VQRRFFMGNQVLKVFAARDDEAAAVALSSLIHALDDLDMVAIVRYAYDKR 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 VQRRFFMGNQVLKVFAARDDEAAAVALSSLIHALDDLDMVAIVRYAYDKR 400
                 .         .         .         .         .
401 ANPQVGVAFPHIKHNYECLVYVQLPFMEDLRQYMFSSLKNSKKYAPTEAQ 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 ANPQVGVAFPHIKHNYECLVYVQLPFMEDLRQYMFSSLKNSKKYAPTEAQ 450
                 .         .         .         .
451 LNAVDALIDSMSLAKKDEKTDTLEDLFPTTKIPNPRFQRLFQ 492
    ||||||||||||||||||||||||||||||||||||||||||
451 LNAVDALIDSMSLAKKDEKTDTLEDLFPTTKIPNPRFQRLFQ 492
```

Fig. 1(Cont.)

```
  1 MVRSGNKAAVVLCMDVGFTMSNSIPGIESPFEQAKKVITMFVQRQVFAEN  50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MVRSGNKAAVVLCMDVGFTMSNSIPGIESPFEQAKKVITMFVQRQVFAEN  50
             .         .         .         .         .
 51 KDEIALVLFGTDGTDNPLSGGDQYQNITVHRHLMLPDFDLLEDIESKIQP 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 KDEIALVLFGTDGTDNPLSGGDQYQNITVHRHLMLPDFDLLEDIESKIQP 100
             .         .         .         .         .
101 GSQQADFLDALIVSMDVIQHETIGKKFEKRHIEIFTDLSSRFSKSQLDII 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 GSQQADFLDALIVSMDVIQHETIGKKFEKRHIEIFTDLSSRFSKSQLDII 150
             .         .         .         .         .
151 IHSLKKCDISLQFFLPFSLGKEDGSGDRGDGPFRLGGHGPSFPLKGITEQ 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 IHSLKKCDISLQFFLPFSLGKEDGSGDRGDGPFRLGGHGPSFPLKGITEQ 200
             .         .         .         .         .
201 QKEGLEIVKMVMISLEGEDGLDEIYSFSESLRKLCVFKKIERHSIHWPCR 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 QKEGLEIVKMVMISLEGEDGLDEIYSFSESLRKLCVFKKIERHSIHWPCR 250
```

Fig. 2.

```
                 .         .         .         .         .
251 LTIGSNLSIRIAAYKSILQERVKKTWTVVDAKTLKKEDIQKETVYCLNDD 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 LTIGSNLSIRIAAYKSILQERVKKTWTVVDAKTLKKEDIQKETVYCLNDD 300

            .         .         .         .         .
301 DETE.............................................. 304
                           ||||
301 DETEVLKEDIIQGFRYGSDIVPFSKVDEEQMKYKSEGKCFSVLGFCKSSQ 350

            .         .         .         .         .
305 ...............LNPPAEVTTKSQIPLSKIKTLFPLIEAKKKDQVTA 339
           ||||||||||||||||||||||||||||||||||||
501 PREPLPPIQQHIWNMLNPPAEVTTKSQIPLSKIKTLFPLIEAKKKDQVTA 550

            .         .         .         .         .
340 QEIFQDNHEDGPTAKKLKTEQGGAHFSVSSLAEGSVTSVGSVNPAENFRV 389
    ||||||||||||||||||||||||||||||||||||||||||||||||||
551 QEIFQDNHEDGPTAKKLKTEQGGAHFSVSSLAEGSVTSVGSVNPAENFRV 600

            .         .         .         .         .
390 LVKQKKASFEEASNQLINHIEQFLDTNETPYFMKSIDCIRAFREEAIKFS 439
    ||||||||||||||||||||||||||||||||||||||||||||||||||
601 LVKQKKASFEEASNQLINHIEQFLDTNETPYFMKSIDCIRAFREEAIKFS 650
```

Fig. 2 (Cont.)

```
440 EEQRFNNFLKALQEKVEIKQLNHFWEIVVQDGITLITKEEASGSSVTAEE 489
    ||||||||||||||||||||||||||||||||||||||||||||||||||
651 EEQRFNNFLKALQEKVEIKQLNHFWEIVVQDGITLITKEEASGSSVTAEE 700

              .         .         .
490 AKKFLAPKDKPSGDTAAVFEEGGDVDDLLDMI 521
    ||||||||||||||||||||||||||||||||
701 AKKFLAPKDKPSGDTAAVFEEGGDVDDLLDMI 732
```

Fig. 2 (Cont.)

```
              .         .         .         .         .
  2 GCGCSSHPEDDWMENIDVCENCHYPIVPLDGKGTLLIRNGSEVRDPLVTY 51
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 GCGCSSHPEDDWMENIDVCENCHYPIVPLDGKGTLLIRNGSEVRDPLVTY 50

 52 EGSNPPASPLQDNLVIALHSYEPSHDGDLGFEKGEQLRILEQSGEWWKAQ 101
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 EGSNPPASPLQDNLVIALHSYEPSHDGDLGFEKGEQLRILEQSGEWWKAQ 100
              .         .         .         .         .
102 SLTTGQEGFIPFNFVAKANSLEPEPWFFKNLSRKDAERQLLAPGNTHGSF 151
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 SLTTGQEGFIPFNFVAKANSLEPEPWFFKNLSRKDAERQLLAPGNTHGSF 150
              .         .         .         .         .
152 LIRESESTAGSFSLSVRDFDQNQGEVVKHYKIRNLDNGGFYISPRITFPG 201
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 LIRESESTAGSFSLSVRDFDQNQGEVVKHYKIRNLDNGGFYISPRITFPG 200
              .         .         .         .         .
202 LHELVRHYTNASDGLCTRLSRPCQTQKPQKPWWEDEWEVPRETLKLVERL 251
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 LHELVRHYTNASDGLCTRLSRPCQTQKPQKPWWEDEWEVPRETLKLVERL 250
```

Fig. 3

```
252 GAGQFGEVWMGYYNGHTKVAVKSLKQGSMSPDAFLAEANLMKQLQHQRLV 301
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 GAGQFGEVWMGYYNGHTKVAVKSLKQGSMSPDAFLAEANLMKQLQHQRLV 300

302 RLYAVVTQEPIYIITEYMENGSLVDFLKTPSGIKLTINKLLDMAAQIAEG 351
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 RLYAVVTQEPIYIITEYMENGSLVDFLKTPSGIKLTINKLLDMAAQIAEG 350

352 MAFIEERNYIHRDLRAANILVSDTLSCKIADFGLARLIEDIHHQVR 397
    ||||||||||||||||||||||||||||||||||||||||  :  |
351 MAFIEERNYIHRDLRAANILVSDTLSCKIADFGLARLIEDNEYTAR 396
```

Fig. 3(Cont.)

```
                 .         .         .         .         .
302 TLKLVERLGAGQFGEVWMGYYNGHTKVAVKSLKQGSMSPDAFLAEANLMK 351
    ||||||||||||||||||||||||||||||||||||||||||||||||||
243 TLKLVERLGAGQFGEVWMGYYNGHTKVAVKSLKQGSMSPDAFLAEANLMK 292
             .         .         .         .         .
352 QLQHQRLVRLYAVVTQEPIYIITEYMENGSLVDFLKTPSGIKLTINKLLD 401
    ||||||||||||||||||||||||||||||||||||||||||||||||||
293 QLQHQRLVRLYAVVTQEPIYIITEYMENGSLVDFLKTPSGIKLTINKLLD 342
             .         .         .         .         .
402 MAAQIAEGMAFIEERNYIHRDLRAANILVSDTLSCKIADFGLARLIEDNE 451
    ||||||||||||||||||||||||||||||||||||||||||||||||||
343 MAAQIAEGMAFIEERNYIHRDLRAANILVSDTLSCKIADFGLARLIEDNE 392
             .         .         .         .         .
452 YTAREGAKFPIKWTAPEAINYGTFTIKSDVWSFGILLTEIVTHGRIPYPG 501
    ||||||||||||||||||||||||||||||||||||||||||||||||||
393 YTAREGAKFPIKWTAPEAINYGTFTIKSDVWSFGILLTEIVTHGRIPYPG 442
             .         .         .         .         .
502 MTNPEVIQNLERGYRMVRPDNCPEELYQLMRLCWKERPEDRPTFDYLRSV 551
    ||||||||||||||||||||||||||||||||||||||||||||||||||
443 MTNPEVIQNLERGYRMVRPDNCPEELYQLMRLCWKERPEDRPTFDYLRSV 492
             .
552 LEDFFTATEGQYQPQP 567
    ||||||||||||||||
493 LEDFFTATEGQYQPQP 508
```

Fig. 4 (Cont.)

```
                  .         .         .         .         .
  2 GCGCSSHPEDDWMENIDVCENCHYPIVPLDGKGTLLIRNGSEVRDPLVTY  51
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 GCGCSSHPEDDWMENIDVCENCHYPIVPLDGKGTLLIRNGSEVRDPLVTY  50

                  .         .         .         .         .
 52 EGSNPPASPLQGDPRQQGLKDKACGSLAVGFHLSPTYFLPGLAFLVPHPV 101
                        |||||||||||
 51 EGSNPPASPLQ.......................................  61

                  .         .         .         .         .
102 TPGFLPIPARFSLTPLVFTDNLVIALHSYEPSHDGDLGFEKGEQLRILEQ 151
              |||||||||||||||||||||||||||||||
 62 ...................DNLVIALHSYEPSHDGDLGFEKGEQLRILEQ  92

                  .         .         .         .         .
152 SGEWWKAQSLTTGQEGFIPFNFVAKANSLEPEPWFFKNLSRKDAERQLLA 201
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 93 SGEWWKAQSLTTGQEGFIPFNFVAKANSLEPEPWFFKNLSRKDAERQLLA 142

                  .         .         .         .         .
202 PGNTHGSFLIRESESTAGSFSLSVRDFDQNQGEVVKHYKIRNLDNGGFYI 251
    ||||||||||||||||||||||||||||||||||||||||||||||||||
143 PGNTHGSFLIRESESTAGSFSLSVRDFDQNQGEVVKHYKIRNLDNGGFYI 192

                  .         .         .         .         .
252 SPRITFPGLHELVRHYTNASDGLCTRLSRPCQTQKPQKPWWEDEWEVPRE 301
    ||||||||||||||||||||||||||||||||||||||||||||||||||
193 SPRITFPGLHELVRHYTNASDGLCTRLSRPCQTQKPQKPWWEDEWEVPRE 242
```

Fig. 4

```
  1 MRIAVICFCLLGITCAIPVKQADSGSSEEKQLYNKYPDAVATWLNPDPSQ 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MRIAVICFCLLGITCAIPVKQADSGSSEEKQLYNKYPDAVATWLNPDPSQ 50
              .         .         .         .         .
 51 KQNLLAPQNAVSSEETNDFKQETLPSKSNESHDHMDDMDDEDDDDHVDSQ 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 KQNLLAPQNAVSSEETNDFKQETLPSKSNESHDHMDDMDDEDDDDHVDSQ 100
              .         .         .         .         .
101 DSIDSNDSDDVDDTDDSHQSDESHHSDESDELVTDFPTDLPATEVFTPVV 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 DSIDSNDSDDVDDTDDSHQSDESHHSDESDELVTDFPTDLPATEVFTPVV 150
              .         .         .
151 PTVDTYDGRGDSVVYGLRSKSKKFRRPDIQVNPLTD 186
    ||||||||||||||||||||||||||||||    ||
151 PTVDTYDGRGDSVVYGLRSKSKKFRRPDIQYPDATD 186
```

Fig. 5

```
62  AEAIPCTLAVSNPHTDAWKSHGLVEVASYCEESRGNNQWVPYISLQER 109
    |  : | | |.|||||||||||||||||||||||||||||||||||||
114 ARDLHC.LLVTNPHTDAWKSHGLVEVASYCEESRGNNQWVPYISLQER 160
```

Fig. 6

```
  1 MRARPQVCEALLFALALQTGVCYGIKWLALSKTPSALALNQTQHCKQLEG 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MRARPQVCEALLFALALQTGVCYGIKWLALSKTPSALALNQTQHCKQLEG 50
             .         .         .         .         .
 51 LVSAQVQLCRSNLELMHTVVHAAREVMKACRRAFADMRWNCSSIELAPNY 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 LVSAQVQLCRSNLELMHTVVHAAREVMKACRRAFADMRWNCSSIELAPNY 100
             .         .         .         .         .
101 LLDLERGTRESAFVYALSAAAISHAIARACTSGDLPGCSCGPVPGEPPGP 150
    |||||||||||||||||||| |||||||||||||||||||||||||||||
101 LLDLERGTRESAFVYALSAATISHAIARACTSGDLPGCSCGPVPGEPPGP 150
             .         .         .         .         .
151 GNRWGRCADNLSYGLLMGAKFSDAPMKVKKTGSQANKLMRLHNSEVGRQA 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 GNRWGRCADNLSYGLLMGAKFSDAPMKVKKTGSQANKLMRLHNSEVGRQA 200
             .         .         .         .         .
201 LRASLEMKCKCHGVSGSCSIRTCWKGLQELQDVAADLKTRYLSATKVVHR 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 LRASLEMKCKCHGVSGSCSIRTCWKGLQELQDVAADLKTRYLSATKVVHR 250
                      .         .
```

Fig. 7

```
251 PMGTRKHLVPKDLDIRPVKDSELVYLQSSPDFCMKNEKVGSHGTQDRQCN 300
    |||||||||||||||||||| |||||||||||||||||||||||||||||
251 PMGTRKHLVPKDLDIRPVKDWELVYLQSSPDFCMKNEKVGSHGTQDRQCN 300
             .         .         .         .         .
301 KTSNGSDSCDLM.......................CCYVTCRRCERTVER 327
    ||||||||||||                       |||||||||||||||
301 KTSNGSDSCDLMCCGRGYNPYTDRVVERCHCKYHWCCYVTCRRCERTVER 350

328 YVCK 331
    ||||
351 YVCK 354
```

Fig. 7(Cont.)

```
  1 MRARPQVCEALLFALALQTGVCYGIKWLALSKTPSALALNQTQHCKQLEG 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MRARPQVCEALLFALALQTGVCYGIKWLALSKTPSALALNQTQHCKQLEG 50
             .         .         .         .         .
 51 LVSAQVQLCRSNLELMHTVVHAAREVMKACRRAFADMRWNCSSIELAPNY 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 LVSAQVQLCRSNLELMHTVVHAAREVMKACRRAFADMRWNCSSIELAPNY 100
             .         .         .         .         .
101 LLDLERGTRESAFVYA.................................. 116
                     ||||||||||||||||
101 LLDLERGTRESAFVYALSAATISHAIARACTSGDLPGCSCGPVPGEPPGP 150
                               .
117 .................................AADLKTRYLSATKVVHR 133
                                     |||||||||||||||||
201 LRASLEMKCKCHGVSGSCSIRTCWKGLQELQDVAADLKTRYLSATKVVHR 250
             .         .         .         .         .
134 PMGTRKHLVPKDLDIRPVKDSELVYLQSSPDFCMKNEKVGSHGTQDRQCN 183
    |||||||||||||||||||| |||||||||||||||||||||||||||||
251 PMGTRKHLVPKDLDIRPVKDWELVYLQSSPDFCMKNEKVGSHGTQDRQCN 300
```

Fig. 8

```
184 KTSNGSDSCDLMCCGRGYNPYTDRVVERCHCKYHWCCYVTCRRCERTVER 233
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 KTSNGSDSCDLMCCGRGYNPYTDRVVERCHCKYHWCCYVTCRRCERTVER 350

    234 YVCK 237
        ||||
    351 YVCK 354
```

Fig. 8(Cont.)

```
   1 MSPFLRIGLSNFDCGSCQSCQGEAVNPYCAVLVKEYVESENGQMYIQKKP 50
     ||||||||||||||||||||||||||||||||||||||||||||||||||
   1 MSPFLRIGLSNFDCGSCQSCQGEAVNPYCAVLVKEYVESENGQMYIQKKP 50
          .         .         .         .         .
  51 TMYPPWDSTFDAHINKGRVMQIIVKGKNVDLISETTVELYSLAERCRKNN 100
     ||||||||||||||||||||||||||||||||||||||||||||||||||
  51 TMYPPWDSTFDAHINKGRVMQIIVKGKNVDLISETTVELYSLAERCRKNN 100
          .         .         .         .         .
 101 GKTEIWLELKPQGRMLMNARYFLEMSDTKDMNEFETEGFFALHQRRGAIK 150
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 101 GKTEIWLELKPQGRMLMNARYFLEMSDTKDMNEFETEGFFALHQRRGAIK 150
          .         .         .         .         .
 151 QAKVHHVKCHEFTATFFPQPTFCSVCHEFVWGLNKQGYQCRQCNAAIHKK 200
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 151 QAKVHHVKCHEFTATFFPQPTFCSVCHEFVWGLNKQGYQCRQCNAAIHKK 200
          .         .         .         .         .
 201 CIDKVIAKCTGSAINSRETMFHKERFKIDMPHRFKVYNYKSPTFCEHCGT 250
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 201 CIDKVIAKCTGSAINSRETMFHKERFKIDMPHRFKVYNYKSPTFCEHCGT 250
          .         .         .         .         .
 251 LLWGLARQGLKCDACGMNVHHRCQTKVANLCGINQKLMAEALAMIESTQQ 300
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 251 LLWGLARQGLKCDACGMNVHHRCQTKVANLCGINQKLMAEALAMIESTQQ 300
```

Fig. 9

```
301 ARCLRDTEQIFREGPVEIGLPCSIKNEARPPCLPTPGKREPQGISWESPL 350
    ||||||||||||||||||||||||||||| ||||||||||||||||||||
301 ARCLRDTEQIFREGPVEIGLPCSIKNEARLPCLPTPGKREPQGISWESPL 350
         .         .         .         .         .
351 DEVDKMCHLPEPELNKERPSLQIKLKIEDFILHKMLGKGSFGKVFLAEFK 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 DEVDKMCHLPEPELNKERPSLQIKLKIEDFILHKMLGKGSFGKVFLAEFK 400
         .         .         .         .         .
401 KTNQFFAIKALKKDVVLMDDDVECTMVEKRVLSLAWEHPFLTHMFCTFQT 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 KTNQFFAIKALKKDVVLMDDDVECTMVEKRVLSLAWEHPFLTHMFCTFQT 450
         .         .         .         .         .
451 KENLFFVMEYLNGGDLMYHIQSCHKFDLSRATFYAAEIILGLQFLHSKGI 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 KENLFFVMEYLNGGDLMYHIQSCHKFDLSRATFYAAEIILGLQFLHSKGI 500
         .         .         .         .         .
501 VYRDLKLDNILLDKDGHIKIADFGMCKENMLGDAKTNTFCGTPDYIAPEI 550
    ||||||||||||||||||||||||||||||||||||||||||||||||||
501 VYRDLKLDNILLDKDGHIKIADFGMCKENMLGDAKTNTFCGTPDYIAPEI 550
```

Fig. 9(Cont.)

```
                  .         .         .
551 LLGQKYNHSVDWWSFGVLLYEMLIGQSPFHGQDEEELFHSIRMDNPFYPR 600
    ||||||||||||||||||||||||||||||||||||||||||||||||||
551 LLGQKYNHSVDWWSFGVLLYEMLIGQSPFHGQDEEELFHSIRMDNPFYPR 600

          .
601 WLEKEAKDLLVKV 613
    ||||||||||||.
601 WLEKEAKDLLVKL 613
```

Fig. 9(Cont.)

```
  1 MPITRMRMRPWLEMQINSNQIPGLIWINKEEMIFQIPWKHAAKHGWDINK 50
    |||| |||||||||||||||||||||||||||| :|||||||||||||||
  1 MPITWMRMRPWLEMQINSNQIPGLIWINKEEMILEIPWKHAAKHGWDINK 50

 51 DACLFRSWAIHTGRYKAGEKEPDPKTWKANFRCAMNSLPDIEEVKDQSRN 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 DACLFRSWAIHTGRYKAGEKEPDPKTWKANFRCAMNSLPDIEEVKDQSRN 100

101 KGSSAVRVYRMLPPLTKNQRKERKSKSSRDAKSKAKRKSCGDSSPDTFSD 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 KGSSAVRVYRMLPPLTKNQRKERKSKSSRDAKSKAKRKSCGDSSPDTFSD 150

151 GLSSSTLPDDHSSYTVPGYMQDLEVEQALTPALSPCAVSSTLPDWHIPVE 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 GLSSSTLPDDHSSYTVPGYMQDLEVEQALTPALSPCAVSSTLPDWHIPVE 200

201 VVPDSTSDLYNFQVSPMPSTSEATTDEDEEGKLPEDIMKLLEQSEWQPTN 250
    ||||||||||||||||||| ||||||||||||||||||||||||||||||
201 VVPDSTSDLYNFQVSPMPSISEATTDEDEEGKLPEDIMKLLEQSEWQPTN 250

251 VDGKGYLLNEPGVQPTSVYGDFSCKEEPEIDSPGG 285
    |||||||||||||||||||||||||||||||||||
251 VDGKGYLLNEPGVQPTSVYGDFSCKEEPEIDSPGG 285
```

Fig. 10

```
  1 MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHPGDL  50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MWSWKCLLFWAVLVTATLCTARPSPTLPEQAQPWGAPVEVESFLVHPGDL  50

 51 LQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGLYA 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 LQLRCRLRDDVQSINWLRDGVQLAESNRTRITGEEVEVQDSVPADSGLYA 100

101 CVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNRMP 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 CVTSSPSGSDTTYFSVNVSDALPSSEDDDDDDDSSSEEKETDNTKPNRMP 150

151 VAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEFKPD 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 VAPYWTSPEKMEKKLHAVPAAKTVKFKCPSSGTPNPTLRWLKNGKEFKPD 200

201 HRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLDVVER 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 HRIGGYKVRYATWSIIMDSVVPSDKGNYTCIVENEYGSINHTYQLDVVER 250

251 SPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKI 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 SPHRPILQAGLPANKTVALGSNVEFMCKVYSDPQPHIQWLKHIEVNGSKI 300
```

Fig. 11

```
301 GPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLS 350
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 GPDNLPYVQILKTAGVNTTDKEMEVLHLRNVSFEDAGEYTCLAGNSIGLS 350
                  .         .         .
351 HHSAWLTVLEALEERPAVMTSPLYLEIIIYCTGAFLISCMVGSVIVYKMK 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 HHSAWLTVLEALEERPAVMTSPLYLEIIIYCTGAFLISCMVGSVIVYKMK 400
        .         .         .         .         .
401 SGTKKSDFHSQMAVHKLAKSIPLRRQVTVSADSSASMNSGVLLVRPSRLS 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 SGTKKSDFHSQMAVHKLAKSIPLRRQVTVSADSSASMNSGVLLVRPSRLS 450
        .         .         .         .         .
451 SSGTPMLAGVSEYELPEDPRWELPRDRLVLGKPLGEGCFGQVVLAEAIGL 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 SSGTPMLAGVSEYELPEDPRWELPRDRLVLGKPLGEGCFGQVVLAEAIGL 500
        .         .         .         .         .
501 DKDKPNRVTKVAVKMLKSDATEKDLSDLISEMEMMKMIGKHKNIINLLGA 550
    ||||||||||||||||||||||||||||||||||||||||||||||||||
501 DKDKPNRVTKVAVKMLKSDATEKDLSDLISEMEMMKMIGKHKNIINLLGA 550
```

Fig. 11(Cont.)

```
551 CTQDGPLYVIVEYASKGNLREYLQARRPPGLEYCYNPSHNPEEQLSSKDL 600
    ||||||||||||||||||||||||||||||||||||||||||||||||||
551 CTQDGPLYVIVEYASKGNLREYLQARRPPGLEYCYNPSHNPEEQLSSKDL 600

601 VSCAYQVARGMEYLASKKCIHRDLAARNVLVTEDNVMKIADFGLARDIHH 650
    ||||||||||||||||||||||||||||||||||||||||||||||||||
601 VSCAYQVARGMEYLASKKCIHRDLAARNVLVTEDNVMKIADFGLARDIHH 650

651 IDYYKKTTNGRLPVKWMAPEALFDRIYTHQSDVWSFGV 688
    ||||||||||||||||||||||||||||||||||||||
651 IDYYKKTTNGRLPVKWMAPEALFDRIYTHQSDVWSFGV 688
```

Fig. 11(Cont.)

```
                  .         .         .         .         .
  2 PKRGKKGAVAEDGDELRTEPEAKKSKTAAKKNDKEAAGEGPALYEDPPDQ 51
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 PKRGKKGAVAEDGDELRTEPEAKKSKTAAKKNDKEAAGEGPALYEDPPDQ 50

                  .         .         .         .         .
 52 KTSPSGKPATLKICSWNVDGLRAWIKKKGLDWVKEEAPDILCLQETKCSE 101
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 KTSPSGKPATLKICSWNVDGLRAWIKKKGLDWVKEEAPDILCLQETKCSE 100

                  .         .         .         .         .
102 NKLPAEELQELPGLSHQYWSAPSDKEGYSGVGLLSRQCPLKVSYGI..... 146
    |||||||||||||||||||||||||||||||||||||||||||||
101 NKLPAELQELPGLSHQYWSAPSDKEGYSGVGLLSRQCPLKVSYGIGDEEH 150

                  .         .         .         .         .
147 ..................AYVPNAGRGLVRLEYRQRWDEAFRKFLKGLAS 178
                      ||||||||||||||||||||||||||||||||
151 DQEGRVIVAEFDSFVLVTAYVPNAGRGLVRLEYRQRWDEAFRKFLKGLAS 200

                  .         .         .         .         .
179 RKPLVLCGDLNVAHEEIDLRNPKGNKKNAGFTPQERQGFGELLQAVPLAD 228
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 RKPLVLCGDLNVAHEEIDLRNPKGNKKNAGFTPQERQGFGELLQAVPLAD 250
```

Fig. 12

```
229 SFRHLYPNTPYAYTFWTYMMNARSKNVGWRLDYFLLSHSLLPALCDSKIR 278
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 SFRHLYPNTPYAYTFWTYMMNARSKNVGWRLDYFLLSHSLLPALCDSKIR 300

279 SKALGSDHCPITLYLAL 295
    |||||||||||||||||
301 SKALGSDHCPITLYLAL 317
```

Fig. 12(Cont.)

```
  2 PKRGKKGAVAEDGDELRTGKGMKSALLPRNCGGGVCHSLDVREPEAKKSK 51
    ||||||||||||||||||                        ||||||||
  1 PKRGKKGAVAEDGDELRT........................EPEAKKSK 26
             .         .         .         .         .
 52 TAAKKNDKEAAGEGPALYEDPPDQKTSPSGKPATLKICSWNVDGLRAWIK 101
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 27 TAAKKNDKEAAGEGPALYEDPPDQKTSPSGKPATLKICSWNVDGLRAWIK 76
             .         .         .         .         .
102 KKGLDWVKEEAPDILCLQETKCSENKLPAELQELPGLSHQYWSAPSDKEG 151
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 77 KKGLDWVKEEAPDILCLQETKCSENKLPAELQELPGLSHQYWSAPSDKEG 126
             .         .         .         .         .
152 YSGVGLLSRQCPLKVSYGIGDEEHDQEGRVIVAEFDSFVLVTAYVPNAGR 201
    ||||||||||||||||||||||||||||||||||||||||||||||||||
127 YSGVGLLSRQCPLKVSYGIGDEEHDQEGRVIVAEFDSFVLVTAYVPNAGR 176
             .         .         .         .         .
202 GLVRLEYRQRWDEAFRKFLKGLASRKPLVLCGDLNVAHEEIDLRNPKGNK 251
    ||||||||||||||||||||||||||||||||||||||||||||||||||
177 GLVRLEYRQRWDEAFRKFLKGLASRKPLVLCGDLNVAHEEIDLRNPKGNK 226
```

Fig. 13

```
252 KNAGFTPQERQGFGELLQAVPLADSFRHLYPNTPYAYTFWTYMMNARSKN 301
    ||||||||||||||||||||||||||||||||||||||||||||||||||
227 KNAGFTPQERQGFGELLQAVPLADSFRHLYPNTPYAYTFWTYMMNARSKN 276

302 VGWRLDYFLLSHSLLPALCDSKIRSKALGSDHCPITLYLAL 342
    |||||||||||||||||||||||||||||||||||||||||
277 VGWRLDYFLLSHSLLPALCDSKIRSKALGSDHCPITLYLAL 317
```

Fig. 13(Cont.)

```
  1 MFQAAERPQEWAMEGPRDGLKKERLLDDRHDSGLDSMKDEEYEQMVKELQ 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MFQAAERPQEWAMEGPRDGLKKERLLDDRHDSGLDSMKDEEYEQMVKELQ 50

 51 EIRLEPQEVPRGSEPWKQQLTEDGDSFLHLAIIHEEKALTMEVIRQVKGD 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 EIRLEPQEVPRGSEPWKQQLTEDGDSFLHLAIIHEEKALTMEVIRQVKGD 100

101 LAFLNFQNNLQQTPLHLAVITNQPEIAEALLGAGCDPELRDFRGNTPLHL 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 LAFLNFQNNLQQTPLHLAVITNQPEIAEALLGAGCDPELRDFRGNTPLHL 150

151 ACEQGCLASVGVLTQSCTTPHLHSILKATNYNGHTCLHLASIHGYLGIVE 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 ACEQGCLASVGVLTQSCTTPHLHSILKATNYNGHTCLHLASIHGYLGIVE 200

201 LLVSLGADVNAQEPCNGRTALHLAVDLQNPDLVSLLLKCGADVNRVTYQG 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 LLVSLGADVNAQEPCNGRTALHLAVDLQNPDLVSLLLKCGADVNRVTYQG 250
```

Fig. 14

```
251 YSPYQLTWGRPSTRIQQQLGQLTLENLQMLPESEDEESYDTESEFTEFTE 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 YSPYQLTWGRPSTRIQQQLGQLTLENLQMLPESEDEESYDTESEFTEFTE 300

301 DEV 303
    ||.
301 DEL 303
```

Fig. 14 (Cont.)

```
  1 MFQAAERPQEWAMEGPRDGLKKERLLDDRHDSGLDSMKDEEYEQMVKELQ  50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MFQAAERPQEWAMEGPRDGLKKERLLDDRHDSGLDSMKDEEYEQMVKELQ  50

 51 EIRLEPQEVPRGSEPWKQQLTEDGDSFLHLAIIHEEKALTMEVIRQVKGD 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 EIRLEPQEVPRGSEPWKQQLTEDGDSFLHLAIIHEEKALTMEVIRQVKGD 100

101 LAFLNFQNNLQQTPLHLAVITNQPEIAEALLGAGCDPELRDFRGNTPLHL 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 LAFLNFQNNLQQTPLHLAVITNQPEIAEALLGAGCDPELRDFRGNTPLHL 150

151 ACEQGCLASVGVLTQSCTTPHLHSILKATNYNG................. 183
              |||||||||||||||||||||||||||||||
151 ACEQGCLASVGVLTQSCTTPHLHSILKATNYNGHTCLHLASIHGYLGIVE 200

184 ...........QEPCNGRTALHLAVDLQNPDLVSLLLKCGADVNRVTYQG 222
               |||||||||||||||||||||||||||||||||||||||
201 LLVSLGADVNAQEPCNGRTALHLAVDLQNPDLVSLLLKCGADVNRVTYQG 250
```

Fig. 15

```
                 .         .         .         .
223 YSPYQLTWGRPSTRIQQQLGQLTLENLQMLPESEDEESYDTESEFTEFTE 272
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 YSPYQLTWGRPSTRIQQQLGQLTLENLQMLPESEDEESYDTESEFTEFTE 300

                      .
273 DELPYDDCVFGGQRLTL 289
    |||||||||||||||||
301 DELPYDDCVFGGQRLTL 317
```

Fig. 15(Cont.)

```
  1 MAGIFYFALFSCLFGICDAVTGSRVYPANEVTLLDSRSVQGELGWIASPL 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MAGIFYFALFSCLFGICDAVTGSRVYPANEVTLLDSRSVQGELGWIASPL 50
             .         .         .         .         .
 51 EGGWEEVSIMDEKNTPIRTYQVCNVMEPSQNNWLRTDWITREGAQRVYIE 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 EGGWEEVSIMDEKNTPIRTYQVCNVMEPSQNNWLRTDWITREGAQRVYIE 100
             .         .         .         .         .
101 IKFTLRDCNSLPGVMGTCKETFNLYYYESDNDKERFIRENQFVKIDTIAA 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 IKFTLRDCNSLPGVMGTCKETFNLYYYESDNDKERFIRENQFVKIDTIAA 150
             .         .         .         .         .
151 DESFTQVDIGDRIMKLNTEIRDVGPLSKKGFYLAFQDVGACIALVSVRVF 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 DESFTQVDIGDRIMKLNTEIRDVGPLSKKGFYLAFQDVGACIALVSVRVF 200
             .         .         .         .         .
201 YKKCPLTVRNLAQFPDTITGADTSSLVEVRGSCVNNSEEKDVPKMYCGAD 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 YKKCPLTVRNLAQFPDTITGADTSSLVEVRGSCVNNSEEKDVPKMYCGAD 250
             .         .         .         .         .
251 GEWLVPIGNCLCNAGHEERSGECQACKIGYYKALSTDATCAKCPPHSYSV 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 GEWLVPIGNCLCNAGHEERSGECQACKIGYYKALSTDATCAKCPPHSYSV 300
```

Fig. 16

```
301 WEGATSCTCDRGFFRADNDAASMPCTRPPSAPLNLISNVNETSVNLEWSS 350
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 WEGATSCTCDRGFFRADNDAASMPCTRPPSAPLNLISNVNETSVNLEWSS 350

351 PQNTGGRQDISYNVVCKKCGAGDPSKCRPCGSGVHYTPQQNGLKTTKVSI 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 PQNTGGRQDISYNVVCKKCGAGDPSKCRPCGSGVHYTPQQNGLKTTKVSI 400

401 TDLLAHTNYTFEIWAVNGVSKYNPNPDQSVSVTVTTNQAAPSSIALVQAK 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 TDLLAHTNYTFEIWAVNGVSKYNPNPDQSVSVTVTTNQAAPSSIALVQAK 450

451 EVTRYSVALAWLEPDRPNGVILEYEVKYYEKDQNERSYRIVRTAARNTDI 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 EVTRYSVALAWLEPDRPNGVILEYEVKYYEKDQNERSYRIVRTAARNTDI 500

501 KGLNPLTSYVFHVRARTAAGYGDFSEPLEVTTNTVPSRIIGDGANSTVLL 550
    ||||||||||||||||||||||||||||||||||||||||||||||||||
501 KGLNPLTSYVFHVRARTAAGYGDFSEPLEVTTNTVPSRIIGDGANSTVLL 550

551 VSVSGSVVLVVILIAAFVISRRRSKYSKAKQEADEEKHLNQGVRTYVDPF 600
    ||||||||||||||||||||||||||||||||||||||||||||||||||
551 VSVSGSVVLVVILIAAFVISRRRSKYSKAKQEADEEKHLNQGVRTYVDPF 600
```

Fig. 16(Cont.)

```
601 TYEDPNQAVREFAKEIDASCIKIEKVIGVGEFGEVCSGRLKVPGKREICV 650
    ||||||||||||||||||||||||||||||||||||||||||||||||||
601 TYEDPNQAVREFAKEIDASCIKIEKVIGVGEFGEVCSGRLKVPGKREICV 650
             .         .         .         .         .
651 AIKTLKAGYTDKQRRDFLSEASIMGQFDHPNIIHLEGVVTKCKPVMIITE 700
    ||||||||||||||||||||||||||||||||||||||||||||||||||
651 AIKTLKAGYTDKQRRDFLSEASIMGQFDHPNIIHLEGVVTKCKPVMIITE 700
             .         .         .         .         .
701 YMENGSLDAFLRKNDGRFTVIQLVGMLRGIGSGMKYLSDMSYVHRDLAAR 750
    ||||||||||||||||||||||||||||||||||||||||||||||||||
701 YMENGSLDAFLRKNDGRFTVIQLVGMLRGIGSGMKYLSDMSYVHRDLAAR 750
             .         .         .         .         .
751 NILVNSNLVCKVSDFGMSRVLEDDPEAAYTTRGGKIPIRWTAPEAIAYRK 800
    ||||||||||||||||||||||||||||||||||||||||||||||||||
751 NILVNSNLVCKVSDFGMSRVLEDDPEAAYTTRGGKIPIRWTAPEAIAYRK 800
             .         .         .         .         .
801 FTSASDVWSYGIVMWEVMSYGERPYWDMSNQD.................. 832
             ||||||||||||||||||||||||||||||||
801 FTSASDVWSYGIVMWEVMSYGERPYWDMSNQDVIKAIEEGYRLPPPMDCP 850
             .         .         .         .         .
833 ...............................................PNT 835
                        |||
851 IALHQLMLDCWQKERSDRPKFGQIVNMLDKLIRNPNSLKRTGTESSRPNT 900
                         .
```

Fig. 16(Cont.)

```
836 ALLDPSSPEFSAVVSVGDWLQAIKMDRYKDNFTAAGYTTLEAVVHVNQED 885
    ||||||||||||||||||||||||||||||||||||||||||||||||||
901 ALLDPSSPEFSAVVSVGDWLQAIKMDRYKDNFTAAGYTTLEAVVHVNQED 950

886 LARIGITAITHQNKILSSVQAMRTQMQQMHGRMVPV 921
    ||||||||||||||||||||||||||||||||||||
951 LARIGITAITHQNKILSSVQAMRTQMQQMHGRMVPV 986
```

Fig. 16(Cont.)

```
  1 MNDFGIKNMDQVAPVANSYRGTLKRQPAFDTFDGSLFAVFPSLNEEQTLQ 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MNDFGIKNMDQVAPVANSYRGTLKRQPAFDTFDGSLFAVFPSLNEEQTLQ 50
             .         .         .         .         .
 51 EVPTGLDSISHDSANCELPLLTPCSKAVMSQALKATFSGF.......... 90
    ||||||||||||||||||||||||||||||||||||||||
 51 EVPTGLDSISHDSANCELPLLTPCSKAVMSQALKATFSGFKKEQRRLGIP 100
             .         .         .         .         .
 91 ...............FWATNEFSLVNVNLQRFGMNGQMLCNLGKERFLEL 125
                   |||||||||||||||||||||||||||||||||||
101 KNPWLWSEQQVCQWLLWATNEFSLVNVNLQRFGMNGQMLCNLGKERFLEL 150
             .         .         .         .         .
126 APDFVGDILWEHLEQMIKENQEKTEDQYEENSHLTSVPHWINSNTLGFGT 175
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 APDFVGDILWEHLEQMIKENQEKTEDQYEENSHLTSVPHWINSNTLGFGT 200
             .         .         .         .         .
176 EQAPYGMQTQNYPKGGLLDSMCPASTPSVLSSEQEFQMFPKSRLSSVSVT 225
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 EQAPYGMQTQNYPKGGLLDSMCPASTPSVLSSEQEFQMFPKSRLSSVSVT 250
             .         .         .         .         .
226 YCSVSQDFPGSNLNLLTNNSGTPKDHDSPENGADSFESSDSLLQSWNSQS 275
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 YCSVSQDFPGSNLNLLTNNSGTPKDHDSPENGADSFESSDSLLQSWNSQS 300
```

Fig. 17

```
276 SLLDVQRVPSFESFEDDCSQSLCLNKPTMSFKDYIQERSDPVEQGKPVIP 325
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 SLLDVQRVPSFESFEDDCSQSLCLNKPTMSFKDYIQERSDPVEQGKPVIP 350

326 AAVLAGFTGSGPIQLWQFLLELLSDKSCQSFISWTGDGWEFKLADPDEVA 375
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 AAVLAGFTGSGPIQLWQFLLELLSDKSCQSFISWTGDGWEFKLADPDEVA 400

376 RRWGKRKNKPKMNYEKLSRGLRYYYDKNIIHKTSGKRYVYRFVCDLQNLL 425
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 RRWGKRKNKPKMNYEKLSRGLRYYYDKNIIHKTSGKRYVYRFVCDLQNLL 450

426 GFTPEELHAILGVQPDTED 444
    |||||||||||||||||||
451 GFTPEELHAILGVQPDTED 469
```

Fig. 17(Cont.)

```
                    .         .         .         :         .
  1 MAGSAMSSKFFLVALAIFFSFAQVVIEANSWWSLGMNNPVQMSEVYIIGA 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MAGSAMSSKFFLVALAIFFSFAQVVIEANSWWSLGMNNPVQMSEVYIIGA 50

 51 QPLCSQLAGLSQGQKKLCHLYQDHMQYIGEGAKTGIKECQYQFRHRRWNC 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 QPLCSQLAGLSQGQKKLCHLYQDHMQYIGEGAKTGIKECQYQFRHRRWNC 100
                    .         .         .         .         .
101 STVDNTSVFGRVMQIGSRETAFTYAVSAAGVVNAMSRACREGELSTCGCS 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 STVDNTSVFGRVMQIGSRETAFTYAVSAAGVVNAMSRACREGELSTCGCS 150
                    .         .         .         .         .
151 RAARPKDLPRDWLWGGCGDNIDYGYRFAKEFVDARERERIHAKGSYESAR 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 RAARPKDLPRDWLWGGCGDNIDYGYRFAKEFVDARERERIHAKGSYESAR 200
                    .         .         .         .         .
201 ILMNLHNNEAGRRTVYNLADVACKCHGVSGSCSLKTCWLQLADFRKVGDA 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 ILMNLHNNEAGRRTVYNLADVACKCHGVSGSCSLKTCWLQLADFRKVGDA 250

251 LKEKYDT 257
    ||||||.
251 LKEKYDS 257
```

Fig. 18

```
                  .         .         .         .         .
  1 MALRRSMGRPGLPPLPLPPPPRLGLLLAESAAAGLKLMGAPVKLTVSQGQ 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MALRRSMGRPGLPPLPLPPPPRLGLLLAESAAAGLKLMGAPVKLTVSQGQ 50

                  .         .         .         .         .
 51 PVKLNCSVEGMEEPDIQWVKDGAVVQNLDQLYIPVSEQHWIGFLSLKSVE 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 PVKLNCSVEGMEEPDIQWVKDGAVVQNLDQLYIPVSEQHWIGFLSLKSVE 100

                  .         .         .         .         .
101 RSDAGRYWCQVEDGGETEISQPVWLTVEGVPFFTVEPKDLAVPPNAPFQL 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 RSDAGRYWCQVEDGGETEISQPVWLTVEGVPFFTVEPKDLAVPPNAPFQL 150

                  .         .         .         .         .
151 SCEAVGPPEPVTIVWWRGTTKIGGPAPSPSVLNVTGVTQSTMFSCEAHNL 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 SCEAVGPPEPVTIVWWRGTTKIGGPAPSPSVLNVTGVTQSTMFSCEAHNL 200

                  .         .         .         .         .
201 KGLASSRTATVHLQALPAAPFNITVTKLSSSNASVAWMPGADGRALLQSC 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 KGLASSRTATVHLQALPAAPFNITVTKLSSSNASVAWMPGADGRALLQSC 250

                  .         .         .         .         .
251 TVQVTQAPGGWEVLAVVVPVPPFTCLLRDLVPATNYSLRVRCANALGPSP 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 TVQVTQAPGGWEVLAVVVPVPPFTCLLRDLVPATNYSLRVRCANALGPSP 300
```

Fig. 19

```
301 YADWVPFQTKGLAPASAPQNLHAIRTDSGLILEWEEVIPEAPLEGPLGPY 350
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 YADWVPFQTKGLAPASAPQNLHAIRTDSGLILEWEEVIPEAPLEGPLGPY 350

351 KLSWVQDNGTQDELTVEGTRANLTGWDPQKDLIVRVCVSNAVGCGPWSQP 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 KLSWVQDNGTQDELTVEGTRANLTGWDPQKDLIVRVCVSNAVGCGPWSQP 400

401 LVVSSHDRAGQQGPPHSRTSWVPVVLGVLTALVTAAALALILLRKRRKET 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 LVVSSHDRAGQQGPPHSRTSWVPVVLGVLTALVTAAALALILLRKRRKET 450

451 RFGQAFDSVMARGEPAVHFRAARSFNRERPERIEATLDSLGISDELKEKL 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 RFGQAFDSVMARGEPAVHFRAARSFNRERPERIEATLDSLGISDELKEKL 500

501 EDVLIPEQQFTLGRMLGKGEFGSVREAQLKQEDGSFVKVAVKMLKADIIA 550
    ||||||||||||||||||||||||||||||||||||||||||||||||||
501 EDVLIPEQQFTLGRMLGKGEFGSVREAQLKQEDGSFVKVAVKMLKADIIA 550

551 SSDIEEFLREAACMKEFDHPHVAKLVGVSLRSRAKGRLPIPMVILPFMKH 600
    ||||||||||||||||||||||||||||||||||||||||||||||||||
551 SSDIEEFLREAACMKEFDHPHVAKLVGVSLRSRAKGRLPIPMVILPFMKH 600
```

Fig. 19(Cont.)

```
601 GDLHAFLLASRIGENPFNLPLQTLIRFMVDIACGMEYLSSRNFIHRDLAA 650
    ||||||||||||||||||||||||||||||||||||||||||||||||||
601 GDLHAFLLASRIGENPFNLPLQTLIRFMVDIACGMEYLSSRNFIHRDLAA 650

651 RNCMLAEDMTVCVADFGLSRKIYSDCRY 678
    ||||||||||||||||||||||||   |
651 RNCMLAEDMTVCVADFGLSRKIYSGDYY 678
```

Fig. 19(Cont.)

```
  1 MCRIAGALRTLLPLLAALLQASVEASGEIALCKTGFPEDVYSAVLSKDVH  50
    |||||||||||||| |||||||||||||||||||||||||||||||||||
  1 MCRIAGALRTLLPLLLALLQASVEASGEIALCKTGFPEDVYSAVLSKDVH  50

 51 EGQPLLNVKFSNCNGKRKVQYESSEPADFKVDEDGMVYAVRSFPLSSEHA 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 EGQPLLNVKFSNCNGKRKVQYESSEPADFKVDEDGMVYAVRSFPLSSEHA 100

101 KFLIYAQDKETQEKWQVAVKLSLKPTLTEESVKESAEVEEIVFPRQFSKH 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 KFLIYAQDKETQEKWQVAVKLSLKPTLTEESVKESAEVEEIVFPRQFSKH 150

151 SGHLQRQKRDWVIPPINLPENSRGPFPQELVRIRSDRDKNLSLRYSVTGP 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 SGHLQRQKRDWVIPPINLPENSRGPFPQELVRIRSDRDKNLSLRYSVTGP 200

201 GADQPPTGIFIINPISGQLSVTKPLDREQIARFHLRAHAVDINGNQVENP 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 GADQPPTGIFIINPISGQLSVTKPLDREQIARFHLRAHAVDINGNQVENP 250

251 IDIVINVIDMNDNRPEFLHQVWNGTVPEGSKPGTYVMTVTAIDADDPNAL 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 IDIVINVIDMNDNRPEFLHQVWNGTVPEGSKPGTYVMTVTAIDADDPNAL 300
```

Fig. 20

```
301 NGMLRYRIVSQAPSTPSPNMFTINNETGDIITVAAGLDREKVQQYTLIIQ 350
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 NGMLRYRIVSQAPSTPSPNMFTINNETGDIITVAAGLDREKVQQYTLIIQ 350
             .         .         .         .         .
351 ATDMEGNPTYGLSNTATAVITVTDVNDNPPEFTAMTFYGEVPENRVDIIV 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 ATDMEGNPTYGLSNTATAVITVTDVNDNPPEFTAMTFYGEVPENRVDIIV 400
             .         .         .         .         .
401 ANLTVTDKDQPHTPAWNAVYRISGGDPTGRFAIQTDPNSNDGLVTVVKPI 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 ANLTVTDKDQPHTPAWNAVYRISGGDPTGRFAIQTDPNSNDGLVTVVKPI 450
             .         .         .         .         .
451 DFETNRMFVLTVAAENQVPLAKGIQHPPQSTATVSVTVIDVNENPYFAPN 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 DFETNRMFVLTVAAENQVPLAKGIQHPPQSTATVSVTVIDVNENPYFAPN 500
             .         .         .         .         .
501 PKIIRQEEGLHAGTMLTTFTAQDPDRYMQQNIRYTKLSDPANWLKIDPVN 550
    ||||||||||||||||||||||||||||||||||||||||||||||||||
501 PKIIRQEEGLHAGTMLTTFTAQDPDRYMQQNIRYTKLSDPANWLKIDPVN 550
             .         .         .         .         .
551 GQITTIAVLDRESPNVKNNIYNATFLASDNGIPPMSGTGTLQIYLLDIND 600
    ||||||||||||||||||||||||||||||||||||||||||||||||||
551 GQITTIAVLDRESPNVKNNIYNATFLASDNGIPPMSGTGTLQIYLLDIND 600
```

Fig. 20(Cont.)

```
601 NAPQVLPQEAETCETPDPNSINITALDYDIDPNAGPFAFDLPLSPVTIKR 650
    ||||||||||||||||||||||||||||||||||||||||||||||||||
601 NAPQVLPQEAETCETPDPNSINITALDYDIDPNAGPFAFDLPLSPVTIKR 650
             .         .         .         .         .
651 NWTITRLNGDFAQLNLKIKFLEAGIYEVPIIITDSGNPPKSNISILRVKV 700
    ||||||||||||||||||||||||||||||||||||||||||||||||||
651 NWTITRLNGDFAQLNLKIKFLEAGIYEVPIIITDSGNPPKSNISILRVKV 700
             .         .         .         .         .
701 CQCDSNGDCTDVDRIVGAGLGTGAIIAILLCIIILLILVLMFVVWMKRRD 750
    ||||||||||||||||||||||||||||||||||||||||||||||||||
701 CQCDSNGDCTDVDRIVGAGLGTGAIIAILLCIIILLILVLMFVVWMKRRD 750
             .         .         .         .         .
751 KERQAKQLLIDPEDDVRDNILKYDEEGGGEEDQDYDLSQLQQPDTVEPDA 800
    ||||||||||||||||||||||||||||||||||||||||||||||||||
751 KERQAKQLLIDPEDDVRDNILKYDEEGGGEEDQDYDLSQLQQPDTVEPDA 800
             .         .         .
801 IKPVGIRRMDERPIHAEPQYPVRSAAPHPGDIGDFINE 838
    ||||||||||||||||||||||||||||||||||||||
801 IKPVGIRRMDERPIHAEPQYPVRSAAPHPGDIGDFINE 838
```

Fig. 20(Cont.)

```
 1 MERVKMINVQRLLEAAEFLERRERECEHGYASSFPSMPSPRLQHSKPPRR 50
   ||||||||||||||||||||||||||||||||||||||||||||||||||
 1 MERVKMINVQRLLEAAEFLERRERECEHGYASSFPSMPSPRLQHSKPPRR 50

51 LSRAQKHSSGSSNTSTANRSTHNELEKNR 79
   ||||||||||.||||||||||||||||||
51 LSRAQKHSSGTSNTSTANRSTHNELEKNR 79
```

Fig. 21

```
 11 NVQILLEAASYLEQIEKENKKCEHGYASSFPSMPSPRLQHSKPPRRLSRA 60
    ||| ||||| :||. |:|   |||||||||||||||||||||||||||||
  8 NVQRLLEAAEFLERRERE...CEHGYASSFPSMPSPRLQHSKPPRRLSRA 54

              .         .         .         .         .
 61 QKHSSGSSNTSTANRSTHNELEKNRRAHLRLCLERLKVLIPLGPDCTRHT 110
    ||||||.|||||||||||||||||||||||||||||||||||||||||||
 55 QKHSSGTSNTSTANRSTHNELEKNRRAHLRLCLERLKVLIPLGPDCTRHT 104

              .         .         .         .         .
111 TLGLLNKAKAHIKKLEEAERKSQHQLENLEREQRFLKWRLEQLQGPQEME 160
    ||||||||||||||||||||||||||||||||||||||||||||||||||
105 TLGLLNKAKAHIKKLEEAERKSQHQLENLEREQRFLKWRLEQLQGPQEME 154

              .         .         .         .         .
161 RIRMDSIGSTISSDRSDSEREEIEVDVESTEFSHGEVDNISTTSISDIDD 210
    ||||||||||||||||||||||||||||||||||||||||||||||||||
155 RIRMDSIGSTISSDRSDSEREEIEVDVESTEFSHGEVDNISTTSISDIDD 204

              .         .
211 HSSLPSIGSDEGYSSASVKLSFTS 234
    ||||||||||||||||||||||||
205 HSSLPSIGSDEGYSSASVKLSFTS 228
```

Fig. 22

```
  1 MESPASSQPASMPQSKGKSKRKKDLRISCMSKPPAPNPTPPRNLDSRTFI  50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MESPASSQPASMPQSKGKSKRKKDLRISCMSKPPAPNPTPPRNLDSRTFI  50
             .         .         .         .         .
 51 TIGDRNFEVEADDLVTISELGRGAYGVVEKVRHAQSGTIMAVKRIRATVN 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 TIGDRNFEVEADDLVTISELGRGAYGVVEKVRHAQSGTIMAVKRIRATVN 100
             .         .         .         .         .
101 SQEQKRLLMDLDINMRTVDCFYTVTFYGALFREGDVWICMELMDTSLDKF 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 SQEQKRLLMDLDINMRTVDCFYTVTFYGALFREGDVWICMELMDTSLDKF 150
             .         .         .         .         .
151 YRKVLDKNMTIPEDILGEIAVSIVRALEHLHSKLSVIHRDVKPSNVLINK 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 YRKVLDKNMTIPEDILGEIAVSIVRALEHLHSKLSVIHRDVKPSNVLINK 200
             .         .         .         .         .
201 EGHVKMCDFGISGYLVDSVAKTMDAGCKPYMAPERINPELNQKGYNVKSD 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 EGHVKMCDFGISGYLVDSVAKTMDAGCKPYMAPERINPELNQKGYNVKSD 250
```

Fig. 23

```
251 VWSLGITTMIEMAILRFPYESWGTPFQQLKQVVEEPSPQLPADRFSPEFVD 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 VWSLGITTMIEMAILRFPYESWGTPFQQLKQVVEEPSPQLPADRFSPEFVD 300

301 FTAQCLRKNPAERMSYLELI 320
    |||||||||||||||||||.
301 FTAQCLRKNPAERMSYLELM 320
```

Fig. 23(Cont.)

```
  1 MPEIRLRHVVSCSSQDSTHCAENLLKADTYRKWRAAKAGEKTISVVLQLE 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MPEIRLRHVVSCSSQDSTHCAENLLKADTYRKWRAAKAGEKTISVVLQLE 50
             .         .         .         .         .
 51 KEEQIHSVDIGNDGSAFVEVLVGSSAGGAGEQDYEVLLVTSSFMSPSESR 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 KEEQIHSVDIGNDGSAFVEVLVGSSAGGAGEQDYEVLLVTSSFMSPSESR 100
             .         .         .         .         .
101 SGSNPNRVRMFGPDKLVRAAAEKRWDRVKIVCSQPYSKDSPFGLSFVRFH 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 SGSNPNRVRMFGPDKLVRAAAEKRWDRVKIVCSQPYSKDSPFGLSFVRFH 150
             .         .         .         .         .
151 SPPDKDEAEAPSQKVTVTKLGQFRVKEEDESANSLRPGALFFSRINKTSP 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 SPPDKDEAEAPSQKVTVTKLGQFRVKEEDESANSLRPGALFFSRINKTSP 200
             .         .         .         .
201 VTASDPAGPSYAAATLQASSAASSASPVSRAIGSTSKPQESP 242
    ||||||||||||||||||||||||||||||||||||||||||
201 VTASDPAGPSYAAATLQASSAASSASPVSRAIGSTSKPQESP 242
```

Fig. 24

```
                  .         .         .         .         .
  1 MPEIRLRHVVSCSSQDSTHCAENLLKADTYRKWRAAKAGEKTISVVLQLE 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MPEIRLRHVVSCSSQDSTHCAENLLKADTYRKWRAAKAGEKTISVVLQLE 50
                  .         .         .         .         .
 51 KEEQIHSVDIGNDGSAFVEVLVGSSAGGAGEQDYEVLLVTSSFMSPSESR 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 KEEQIHSVDIGNDGSAFVEVLVGSSAGGAGEQDYEVLLVTSSFMSPSESR 100
                  .         .         .         .         .
101 SGSNPNRVRMFGPDKLVRAAAEKRWDRVKIVCSQPYSKDSPFGLSFVRFH 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 SGSNPNRVRMFGPDKLVRAAAEKRWDRVKIVCSQPYSKDSPFGLSFVRFH 150
                  .         .         .         .         .
151 SPPDKDEAEAPSQKVTVTKLGQFRVKEEDESANSLRPGALFFSRINKTSP 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 SPPDKDEAEAPSQKVTVTKLGQFRVKEEDESANSLRPGALFFSRINKTSP 200
                  .         .         .         .         .
201 VTASDPAGPSYAAATLQASSAASSASPVSRAIGSTSKPQESS......DF 244
    |||||||||||||||||||||||||||||||||||||||||       |
201 VTASDPAGPSYAAATLQASSAASSASPVSRAIGSTSKPQESPKGKRKLDL 250
                  .         .
245 GGVEEERSWRPQSIPIPSAP 264
       |..   :| .   || |
251 NQEEKKTPSKPPAQLSPSVP 270
```

Fig. 25

```
  1 MPEIRLRHVVSCSSQDSTHCAENLLKADTYRKWRAAKAGEKTISVVLQLE 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MPEIRLRHVVSCSSQDSTHCAENLLKADTYRKWRAAKAGEKTISVVLQLE 50
              .         .         .         .         .
 51 KEEQIHSVDIGNDGSAFVEVLVGSSAGGAGEQDYEVLLVTSSFMSPSESR 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 KEEQIHSVDIGNDGSAFVEVLVGSSAGGAGEQDYEVLLVTSSFMSPSESR 100
              .         .         .         .         .
101 SGSNPNRVRMFGPDKLVRAAAEKRWDRVKIVCSQPYSKDSPFGLSFVRFH 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 SGSNPNRVRMFGPDKLVRAAAEKRWDRVKIVCSQPYSKDSPFGLSFVRFH 150
              .         .         .         .         .
151 SPPDKDEAEAPSQKVTVTKLGQFRVKEEDESANSLRLEDYMSDRVQFV.. 198
       |||||||||||||||||||||||||||||||||         |:
151 SPPDKDEAEAPSQKVTVTKLGQFRVKEEDESANSLRPGALFFSRINKTSP 200
              .         .
199 ITAQE.WDPSFEEALMDNPSLA 219
    :|| :   ||:  | :  | |
201 VTASDPAGPSYAAATLQASSAA 222
```

Fig. 26

```
  1 MPEIRLRHVVSCSSQDSTHCAENLLKADTYRKWRAAKAGEKTISVVLQLE 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MPEIRLRHVVSCSSQDSTHCAENLLKADTYRKWRAAKAGEKTISVVLQLE 50
             .         .         .         .         .
 51 KEEQIHSVDIGNDGSAFVEVLVGSSAGGAGEQDYEVLLVTSSFMSPSESR 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 KEEQIHSVDIGNDGSAFVEVLVGSSAGGAGEQDYEVLLVTSSFMSPSESR 100
             .         .         .         .         .
101 SGSNPNRVRMFGPDKLVRAAAEKRWDRVKIVCSQPYSKDSPFGLSFVRFH 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 SGSNPNRVRMFGPDKLVRAAAEKRWDRVKIVCSQPYSKDSPFGLSFVRFH 150
             .         .         .         .         .
151 SPPDKDEAEAPSQKVTVTKLGQFRVKEEDESANSLRPGALFFSRINKTSP 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 SPPDKDEAEAPSQKVTVTKLGQFRVKEEDESANSLRPGALFFSRINKTSP 200
             .         .         .         .         .
201 VTASDPAGPSYAAATLQASSAASSASPVSRAIGSTSKPQESPKGKRKLDL 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 VTASDPAGPSYAAATLQASSAASSASPVSRAIGSTSKPQESPKGKRKLDL 250
             .         .         .         .         .
251 NQEEKKTPSKPPAQLSPSVPKRPKLPAPTRTPATAPVPARAQGAVTGKPR 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 NQEEKKTPSKPPAQLSPSVPKRPKLPAPTRTPATAPVPARAQGAVTGKPR 300
```

Fig. 27

```
              .         .         .         .         .
301 GEGTEPRRPRAGPEELGKILQGVVVVLSGFQNPFRSELRDKALELGAKYR 350
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 GEGTEPRRPRAGPEELGKILQGVVVVLSGFQNPFRSELRDKALELGAKYR 350
              .         .         .         .         .
351 PDWTRDSTHLICAFANTPKYSQVLGLGGRIVRKEWVLDCHRMRRRLPSRR 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 PDWTRDSTHLICAFANTPKYSQVLGLGGRIVRKEWVLDCHRMRRRLPSRR 400
              .         .         .         .         .
401 YLMAGPGSSSEEDEASHSGGSGDEAPKLPQKQPQTKTKPTQAAGPSSPQK 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 YLMAGPGSSSEEDEASHSGGSGDEAPKLPQKQPQTKTKPTQAAGPSSPQK 450
              .         .         .         .         .
451 PPTPEETKAASPVLQEDIDIEGVQSEGQDNGAEDSGDTEDELRRVAEQKE 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 PPTPEETKAASPVLQEDIDIEGVQSEGQDNGAEDSGDTEDELRRVAEQKE 500
              .         .         .         .
501 HRLPPGQEENGEDPYAGSTDENTDSEEHQEPPDLPVPELPRFLPGQ 546
    |||||||||||||||||||||||||||||||||||||||| |  |.
501 HRLPPGQEENGEDPYAGSTDENTDSEEHQEPPDLPVPELPDFFQGK 546
```

Fig. 27(Cont.)

```
                   .         .         .         .         .
  1 MAGAIASRMSFSSLKRKQPKTFTVRIVTMDAEMEFNCEMKWKGKDLFDLV  50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MAGAIASRMSFSSLKRKQPKTFTVRIVTMDAEMEFNCEMKWKGKDLFDLV  50
                   .         .         .         .         .
 51 CRTLGLRETWFFGLQYTIKDTVAWLKMDKKVLDHDVSKEEPVTFHFLAKF 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 CRTLGLRETWFFGLQYTIKDTVAWLKMDKKVLDHDVSKEEPVTFHFLAKF 100
                   .         .         .         .         .
101 YPENAEEELVQEITQHLFFLQVKKQILDEKIYCPPEASVLLASYAVQAKY 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 YPENAEEELVQEITQHLFFLQVKKQILDEKIYCPPEASVLLASYAVQAKY 150
                   .         .         .         .         .
151 GDYDPSVHKRGFLAQEELLPKRVINLYQMTPEMWEERITAWYAEHRGRAR 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 GDYDPSVHKRGFLAQEELLPKRVINLYQMTPEMWEERITAWYAEHRGRAR 200
                   .         .         .         .         .
201 DEAEMEYLKIAQDLEMYGVNYFAIRNKKGTELLLGVDALGLHIYDPENRL 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 DEAEMEYLKIAQDLEMYGVNYFAIRNKKGTELLLGVDALGLHIYDPENRL 250
                   .         .         .         .         .
251 TPKISFPWKNEIRNISYSDKEFTIKPLDKKIDVFKFNSSKLRVNKLILQL 300
    |||||||| |||||||||||||||||||||||||||||||||||||||||
251 TPKISFPW.NEIRNISYSDKEFTIKPLDKKIDVFKFNSSKLRVNKLILQL 299
```

Fig.28

```
                  .         .         .         .         .
301 CIGNHDLFMRRRKADSLEVQQMKAQAREEKARK................. 333
    |||||||||||||||||||||||||||||||||
300 CIGNHDLFMRRRKADSLEVQQMKAQAREEKARKQMERQRLAREKQMREEA 349

                  .         .         .         .         .
334 ............QMKEEATMANEALMRSEETADLLAEKAQITEEEAKLLA 371
                ||||||||||||||||||||||||||||||||||||||
350 ERTRDELERRLLQMKEEATMANEALMRSEETADLLAEKAQITEEEAKLLA 399

                  .         .         .         .         .
372 QKAAEAEQEMQRIKATAIRTEEEKRLMEQKVLEAEVLALKMAEESERRAK 421
    ||||||||||||||||||||||||||||||||||||||||||||||||||
400 QKAAEAEQEMQRIKATAIRTEEEKRLMEQKVLEAEVLALKMAEESERRAK 449

                  .         .         .         .         .
422 EADQLKQDLQEAREAERRAKQKLLEIATKPTYPPMNPIPAPLPPDIPSFN 471
    ||||||||||||||||||||||||||||||||||||||||||||||||||
450 EADQLKQDLQEAREAERRAKQKLLEIATKPTYPPMNPIPAPLPPDIPSFN 499

                  .         .         .         .         .
472 LIGDSLSFDFKDTDMKRLSMEIEKEKVEYMEKSKHLQEQLNELKTEIEAL 521
    ||||||||||||||||||||||||||||||||||||||||||||||||||
500 LIGDSLSFDFKDTDMKRLSMEIEKEKVEYMEKSKHLQEQLNELKTEIEAL 549

                  .         .         .         .
522 KLKERETALDILHNENSDRGGSSKHNTIKKLTLQSAKSRVAFFEEL 567
    ||||||||||||||||||||||||||||||||||||||||||||||
550 KLKERETALDILHNENSDRGGSSKHNTIKKLTLQSAKSRVAFFEEL 595
```

Fig.28(Cont.)

```
  1 MRERFDRFLHEKNCMTDLLAKLEAKTGVNRSFIALGVIGLVALYLVFGYG 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MRERFDRFLHEKNCMTDLLAKLEAKTGVNRSFIALGVIGLVALYLVFGYG 50
              .         .         .         .         .
 51 ASLLCNLIGFGYPAYISIKAIESPNKEDDTQWLTYWVVYGVFSIAEFFSD 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 ASLLCNLIGFGYPAYISIKAIESPNKEDDTQWLTYWVVYGVFSIAEFFSD 100
                       .
                  101 IFLSWFPFYYMLK 113
                      |||||||||||||
                  101 IFLSWFPFYYMLK 113
```

Fig. 29

```
  1 MDLEGDRNGGAKKKNFFKLNNKSEKDKKEKKPTVSVFSMFRYSNWLDKLY 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MDLEGDRNGGAKKKNFFKLNNKSEKDKKEKKPTVSVFSMFRYSNWLDKLY 50
             .         .         .         .         .
 51 MVVGTLAAIIHGAGLPLMMLVFGEMTDIFANAGNLEDLMSNITNRSDIND 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 MVVGTLAAIIHGAGLPLMMLVFGEMTDIFANAGNLEDLMSNITNRSDIND 100
             .         .         .         .         .
101 TGFFMNLEEDMTRYAYYYSGIGAGVLVAAYIQVSFWCLAAGRQIHKIRKQ 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 TGFFMNLEEDMTRYAYYYSGIGAGVLVAAYIQVSFWCLAAGRQIHKIRKQ 150
             .         .         .         .         .
151 FFHAIMRQEIGWFDVHDVGELNTRLTDDVSKINEVIGDKIGMFFQSMATF 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 FFHAIMRQEIGWFDVHDVGELNTRLTDDVSKINEVIGDKIGMFFQSMATF 200
             .         .         .         .         .
201 FTGFIVGFTRGWKLTLVILAISPVLGLSAAVWAKILSSFTDKELLAYAKA 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 FTGFIVGFTRGWKLTLVILAISPVLGLSAAVWAKILSSFTDKELLAYAKA 250
             .         .         .         .         .
251 GAVAEEVLAAIRTVIAFGGQKKELERYNKNLEEAKRIGIKKAITANISIG 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 GAVAEEVLAAIRTVIAFGGQKKELERYNKNLEEAKRIGIKKAITANISIG 300
```

Fig. 30

```
301 AAFLLIYASYALAFWYGTTLVLSGEYSIGQVLTVFFSVLIGAFSVGQASP 350
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 AAFLLIYASYALAFWYGTTLVLSGEYSIGQVLTVFFSVLIGAFSVGQASP 350
        .         .         .         .         .
351 SIEAFANARGAAYEIFKIIDNKPSIDSYSKSGHKPDNIKGNLEFRNVHFS 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 SIEAFANARGAAYEIFKIIDNKPSIDSYSKSGHKPDNIKGNLEFRNVHFS 400
        .         .         .         .         .
401 YPSRKEVKILKGLNLKVQSGQTVALVGNSGCGKSTTVQLMQRLYDPTEGM 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 YPSRKEVKILKGLNLKVQSGQTVALVGNSGCGKSTTVQLMQRLYDPTEGM 450
        .         .         .         .         .
451 VSVDGQDIRTINVRFLREIIGVVSQEPVLFATTIAENIRYGRENVTMDEI 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 VSVDGQDIRTINVRFLREIIGVVSQEPVLFATTIAENIRYGRENVTMDEI 500
        .         .         .         .         .
501 EKAVKEANAYDFIMKLPHKFDTLVGERGAQLSGGQKQRIAIARALVRNPK 550
    ||||||||||||||||||||||||||||||||||||||||||||||||||
501 EKAVKEANAYDFIMKLPHKFDTLVGERGAQLSGGQKQRIAIARALVRNPK 550
        .         .         .         .         .
551 ILLLDEATSALDTESEAVVQVALDKARKGRTTIVIAHRLSTVRNADVIAG 600
    ||||||||||||||||||||||||||||||||||||||||||||||||||
551 ILLLDEATSALDTESEAVVQVALDKARKGRTTIVIAHRLSTVRNADVIAG 600
```

Fig. 30(Cont.)

```
601 FDDGVIVEKGNHDELMKEKGIYFKLVTMQTAGNEVELENAADESKSEIDA 650
    ||||||||||||||||||||||||||||||||||||||||||||||||||
601 FDDGVIVEKGNHDELMKEKGIYFKLVTMQTAGNEVELENAADESKSEIDA 650
             .         .         .         .         .
651 LEMSSNDSRSSLIRKRSTRRSVRGSQAQDRKLSTKEALDESIPPVSFWRI 700
    ||||||||||||||||||||||||||||||||||||||||||||||||||
651 LEMSSNDSRSSLIRKRSTRRSVRGSQAQDRKLSTKEALDESIPPVSFWRI 700
             .         .         .         .         .
701 MKLNLTEWPYFVVGVFCAIINGGLQPAFAIIFSKIIGVFTRIDDPETKRQ 750
    ||||||||||||||||||||||||||||||||||||||||||||||||||
701 MKLNLTEWPYFVVGVFCAIINGGLQPAFAIIFSKIIGVFTRIDDPETKRQ 750
             .         .         .         .         .
751 NSNLFSLLFLALGIISFITFFLQGFTFGKAGEILTKRLRYMVFRSMLRQD 800
    ||||||||||||||||||||||||||||||||||||||||||||||||||
751 NSNLFSLLFLALGIISFITFFLQGFTFGKAGEILTKRLRYMVFRSMLRQD 800
             .         .         .         .         .
801 VSWFDDPKNTTGALTTRLANDAAQVKGAIGSRLAVITQNIANLGTGIIIS 850
    ||||||||||||||||||||||||||||||||||||||||||||||||||
801 VSWFDDPKNTTGALTTRLANDAAQVKGAIGSRLAVITQNIANLGTGIIIS 850
             .         .         .         .         .
851 FIYGWQLTLLLLAIVPIIAIAGVVEMKMLSGQALKDKKELEGAGKIATEA 900
    ||||||||||||||||||||||||||||||||||||||||||||||||||
851 FIYGWQLTLLLLAIVPIIAIAGVVEMKMLSGQALKDKKELEGAGKIATEA 900
```

Fig. 30(Cont.)

```
901  IENFRTVVSLTQEQKFEHMYAQSLQVPYRNSLRKAHIFGITFSFTQAMMY  950
     ||||||||||||||||||||||||||||||||||||||||||||||||||
901  IENFRTVVSLTQEQKFEHMYAQSLQVPYRNSLRKAHIFGITFSFTQAMMY  950
              .         .         .         .         .
951  FSYAGCFRFGAYLVAHKLMSFEDVLLVFSAVVFGAMAVGQVSSFAPDYAK  1000
     ||||||||||||||||||||||||||||||||||||||||||||||||||
951  FSYAGCFRFGAYLVAHKLMSFEDVLLVFSAVVFGAMAVGQVSSFAPDYAK  1000
              .         .         .         .         .
1001 AKISAAHIIMIIEKTPLIDSYSTEGLMPNTLEGNVTFGEVVFNYPTRPDI  1050
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1001 AKISAAHIIMIIEKTPLIDSYSTEGLMPNTLEGNVTFGEVVFNYPTRPDI  1050
              .         .         .         .         .
1051 PVLQGLSLEVKKGQTLALVGSSGCGKSTVVQLLERFYDPLAGKVLLDGKE  1100
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1051 PVLQGLSLEVKKGQTLALVGSSGCGKSTVVQLLERFYDPLAGKVLLDGKE  1100
              .         .         .         .         .
1101 IKRLNVQWLRAHLGIVSQEPILFDCSIAENIAYGDNSRVVSQEEIVRAAK  1150
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1101 IKRLNVQWLRAHLGIVSQEPILFDCSIAENIAYGDNSRVVSQEEIVRAAK  1150
              .         .         .         .         .
1151 EANIHAFIESLPNKYSTKVGDKGTQLSGGQKQRIAIARALVRQPHILLLD  1200
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1151 EANIHAFIESLPNKYSTKVGDKGTQLSGGQKQRIAIARALVRQPHILLLD  1200
```

Fig. 30(Cont.)

```
1201 EATSALDTESEKVVQEALDKAREGRTCIVIAHRLSTIQNADLIVVFQNGR 1250
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1201 EATSALDTESEKVVQEALDKAREGRTCIVIAHRLSTIQNADLIVVFQNGR 1250

          .         .
1251 VKEHGTHQQLLAQKGIYFSMVSVQAGT 1277
     |||||||||||||||||||||||||||
1251 VKEHGTHQQLLAQKGIYFSMVSVQAGT 1277
```

Fig. 30(Cont.)

```
  1 MDLEGDRNGGAKKKNFFKLNNKSEKDKKEKKPTVSVFSMFRYSNWLDKLY 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MDLEGDRNGGAKKKNFFKLNNKSEKDKKEKKPTVSVFSMFRYSNWLDKLY 50
             .         .         .         .         .
 51 MVVGTLAAIIHGAGLPLMMLVFGEMTDIFANAGNLEDLMSNITNRSDIND 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 MVVGTLAAIIHGAGLPLMMLVFGEMTDIFANAGNLEDLMSNITNRSDIND 100
             .         .         .         .         .
101 TGFFMNLEEDMTRYAYYYSGIGAGVLVAAYIQVSFWCLAAGRQIHKIRKQ 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 TGFFMNLEEDMTRYAYYYSGIGAGVLVAAYIQVSFWCLAAGRQIHKIRKQ 150
             .         .         .         .         .
151 FFHAIMRQEIGWFDVHDVGELNTRLTDDVSKINEGIGDKIGMFFQSMATF 200
    |||||||||||||||||||||||||||||||||| |||||||||||||||
151 FFHAIMRQEIGWFDVHDVGELNTRLTDDVSKINEVIGDKIGMFFQSMATF 200
             .         .         .         .         .
201 FTGFIVGFTRGWKLTLVILAISPVLGLSAAVWAKILSSFTDKELLAYAKA 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 FTGFIVGFTRGWKLTLVILAISPVLGLSAAVWAKILSSFTDKELLAYAKA 250
             .         .         .         .         .
251 GAVAEEVLAAIRTVIAFGGQKKELERYNKNLEEAKRIGIKKAITANISIG 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 GAVAEEVLAAIRTVIAFGGQKKELERYNKNLEEAKRIGIKKAITANISIG 300
```

Fig. 31

```
301 AAFLLIYASYALAFWYGTTLVLSGEYSIGQVLTVFFSVLIGAFSVGQASP 350
    ||||||||||||||||||||||||||||||||||||||||||||||||||
301 AAFLLIYASYALAFWYGTTLVLSGEYSIGQVLTVFFSVLIGAFSVGQASP 350
             .         .         .         .         .
351 SIEAFANARGAAYEIFKIIDNKPSIDSYSKSGHKPDNIKGNLEFRNVHFS 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 SIEAFANARGAAYEIFKIIDNKPSIDSYSKSGHKPDNIKGNLEFRNVHFS 400
             .         .         .         .         .
401 YPSRKEVKILKGLNLKVQSGQTVALVGNSGCGKSTTVQLMQRLYDPTEGM 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 YPSRKEVKILKGLNLKVQSGQTVALVGNSGCGKSTTVQLMQRLYDPTEGM 450
             .         .         .         .         .
451 VSVDGQDIRTINVRFLREIIGVVSQEPVLFATTIAENIRYGRENVTMDEI 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 VSVDGQDIRTINVRFLREIIGVVSQEPVLFATTIAENIRYGRENVTMDEI 500
             .         .         .         .         .
501 EKAVKEANAYDFIMKLPHKFDTLVGERGAQLSGGQKQRIAIARALVRNPK 550
    ||||||||||||||||||||||||||||||||||||||||||||||||||
501 EKAVKEANAYDFIMKLPHKFDTLVGERGAQLSGGQKQRIAIARALVRNPK 550
             .         .
551 ILLLDEATSALDTESEAEVQAALDKVSR 578
    ||||||||||||||||| || ||||  :
551 ILLLDEATSALDTESEAVVQVALDKARK 578
```

Fig. 31(Cont.)

```
  1 MSRSKRDNNFYSVEIGDSTFTVLKRYQNLKPIGSGAQGIVCAAYDAILER 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MSRSKRDNNFYSVEIGDSTFTVLKRYQNLKPIGSGAQGIVCAAYDAILER 50
             .         .         .         .         .
 51 NVAIKKLSRPFQNQTHAKRAYRELVLMKCVNHKNIIGLLNVFTPQKSLEE 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 NVAIKKLSRPFQNQTHAKRAYRELVLMKCVNHKNIIGLLNVFTPQKSLEE 100
             .         .         .         .         .
101 FQDVYIVMELMDANLCQVIQMELDHERMSYLLYQMLCGIKHLHSAGIIHR 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 FQDVYIVMELMDANLCQVIQMELDHERMSYLLYQMLCGIKHLHSAGIIHR 150
             .         .         .         .         .
151 DLKPSNIVVKSDCTLKILDFGLARTAGTSFMMTPYVVTRYYRAPEVILGM 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 DLKPSNIVVKSDCTLKILDFGLARTAGTSFMMTPYVVTRYYRAPEVILGM 200

201 GYKENTE 207
    ||||| :
201 GYKENVD 207
```

Fig. 32

```
  1 MSRSKRDNNFYSVEIGDSTFTVLKRYQNLKPIGSGAQGIVCAAYDAILER 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MSRSKRDNNFYSVEIGDSTFTVLKRYQNLKPIGSGAQGIVCAAYDAILER 50
             .         .         .         .         .
 51 NVAIKKLSRPFQNQTHAKRAYRELVLMKCVNHKNIIGLLNVFTPQKSLEE 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 NVAIKKLSRPFQNQTHAKRAYRELVLMKCVNHKNIIGLLNVFTPQKSLEE 100
             .         .         .         .         .
101 FQDVYIVMELMDANLCQVIQMELDHERMSYLLYQMLCGIKHLHSAGIIHR 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 FQDVYIVMELMDANLCQVIQMELDHERMSYLLYQMLCGIKHLHSAGIIHR 150
             .         .         .         .         .
151 DLKPSNIVVKSDCTLKILDFGLARTAGTSFMMTPYVVTRYYRAPEVILGM 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 DLKPSNIVVKSDCTLKILDFGLARTAGTSFMMTPYVVTRYYRAPEVILGM 200
             .         .         .         .         .
201 GYKENVDLWSVGCIMGEMVCHKILFPGRDYIDQWNKVIEQLGTPCPEFMK 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 GYKENVDLWSVGCIMGEMVCHKILFPGRDYIDQWNKVIEQLGTPCPEFMK 250
             .         .         .         .
251 KLQPTVRTYVENRPKYAGYSFEKLFPDVLFPADSEHNKLKASQ 293
    |||||||||||||||||||||||||||||||||||||||||||
251 KLQPTVRTYVENRPKYAGYSFEKLFPDVLFPADSEHNKLKASQ 293
```

Fig. 33

```
  1 MSRSKRDNNFYSVEIGDSTFTVLKRYQNLKPIGSGAQGIVCAAYDAILER 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MSRSKRDNNFYSVEIGDSTFTVLKRYQNLKPIGSGAQGIVCAAYDAILER 50
             .         .         .         .         .
 51 NVAIKKLSRPFQNQTHAKRAYRELVLMKCVNHKNIIGLLNVFTPQKSLEE 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 NVAIKKLSRPFQNQTHAKRAYRELVLMKCVNHKNIIGLLNVFTPQKSLEE 100
             .         .         .         .         .
101 FQDVYIVMELMDANLCQVIQMELDHERMSYLLYQMLCGIKHLHSAGIIHR 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 FQDVYIVMELMDANLCQVIQMELDHERMSYLLYQMLCGIKHLHSAGIIHR 150
             .         .         .         .         .
151 DLKPSNIVVKSDCTLKILDFGLARTAGTSFMMTPYVVTRYYRAPEVILGM 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 DLKPSNIVVKSDCTLKILDFGLARTAGTSFMMTPYVVTRYYRAPEVILGM 200
             .         .         .         .         .
201 GYKENVDLWSVGCIMGEMVCHKILFPGRDYIDQWNKVIEQLGTPCPEFMK 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 GYKENVDLWSVGCIMGEMVCHKILFPGRDYIDQWNKVIEQLGTPCPEFMK 250
```

Fig. 34

```
               .         .         .         .
251 KLQPTVRTYVENRPKYAGYSFEKLFPDVLFPADSEHNKLKASQARDLLSK 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 KLQPTVRTYVENRPKYAGYSFEKLFPDVLFPADSEHNKLKASQARDLLSK 300

               .         .         .
301 MLVIDASKRISVDEALQHPYINVWYDPSEAEARSCKL 337
    ||||||||||||||||||||||||||||||||   |:
301 MLVIDASKRISVDEALQHPYINVWYDPSEAEAPPPKI 337
```

Fig. 34(Cont.)

```
  7 arsgfyrqevtktawevravyrdlqpvgsgaygavcsavdgrtgakvaik 56
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 ARSGFYRQEVTKTAWEVRAVYRDLQPVGSGAYGAVCSAVDGRTGAKVAIK 50
              .         .         .         .         .
 57 klyrpfqselfakrayrelrllkhmrhenviglldvftpdetlddftdfy 106
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 KLYRPFQSELFAKRAYRELRLLKHMRHENVIGLLDVFTPDETLDDFTDFY 100
              .         .         .         .         .
107 lvmpfmgtdlgklmkheklgedriqflvyqmlkglryihaagiihrdlkp 156
    ||||||||||||||||||||||||||||||||||||||||||||||  . |
101 LVMPFMGTDLGKLMKHEKLGEDRIQFLVYQMLKGLRYIHAAGIIHR.VSP 149

157 gnlavne 163
    |  | .:
150 GGEAAHQ 156
```

Fig. 35

```
  1 MSPFLRIGLSNFDCGSCQSCQGEAVNPYCAVLVKEYVESENGQMYIQKKP  50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MSPFLRIGLSNFDCGSCQSCQGEAVNPYCAVLVKEYVESENGQMYIQKKP  50
             .         .         .         .         .
 51 TMYPPWDSTFDAHINKGRVMQIIVKGKNVDLISETTVELYSLAERCRKNN 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 TMYPPWDSTFDAHINKGRVMQIIVKGKNVDLISETTVELYSLAERCRKNN 100
             .         .         .         .         .
101 GKTEIWLELKPQGRMLMNARYFLEMSDTKDMNEFETEGFFALHQRRGAIK 150
    ||||||||||||||||||||||||||||||||||||||||||||||||||
101 GKTEIWLELKPQGRMLMNARYFLEMSDTKDMNEFETEGFFALHQRRGAIK 150
             .         .         .         .         .
151 QAKVHHVKCHEFTATFFPQPTFCSVCHEFVWGLNKQGYQCRQCNAAIHKK 200
    ||||||||||||||||||||||||||||||||||||||||||||||||||
151 QAKVHHVKCHEFTATFFPQPTFCSVCHEFVWGLNKQGYQCRQCNAAIHKK 200
             .         .         .         .         .
201 CIDKVIAKCTGSAINSRETMFHKERFKIDMPHRFKVYNYKSPTFCEHCGT 250
    ||||||||||||||||||||||||||||||||||||||||||||||||||
201 CIDKVIAKCTGSAINSRETMFHKERFKIDMPHRFKVYNYKSPTFCEHCGT 250
```

Fig. 36

```
251 LLWGLARQGLKCDACGMNVHHRCQTKVANLCGINQKLMAEALAMIESTQQ 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||
251 LLWGLARQGLKCDACGMNVHHRCQTKVANLCGINQKLMAEALAMIESTQQ 300

301 ARCLRDTEQIFREGPVEIGLPCSIKNEARPPCLPTPGKREPQGISWESPL 350
    ||||||||||||||||||||||||||||| ||||||||||||||||||||
301 ARCLRDTEQIFREGPVEIGLPCSIKNEARLPCLPTPGKREPQGISWESPL 350
             .         .         .         .         .
351 DEVDKMCHLPEPELNKERPSLQIKLKIEDFILHKMLGKGSFGKVFLAEFK 400
    ||||||||||||||||||||||||||||||||||||||||||||||||||
351 DEVDKMCHLPEPELNKERPSLQIKLKIEDFILHKMLGKGSFGKVFLAEFK 400
             .         .         .         .         .
401 KTNQFFAIKALKKDVVLMDDDVECTMVEKRVLSLAWEHPFLTHMFCTFQT 450
    ||||||||||||||||||||||||||||||||||||||||||||||||||
401 KTNQFFAIKALKKDVVLMDDDVECTMVEKRVLSLAWEHPFLTHMFCTFQT 450
             .         .         .         .         .
451 KENLFFVMEYLNGGDLMYHIQSCHKFDLSRATFYAAEIILGLQFLHSKGI 500
    ||||||||||||||||||||||||||||||||||||||||||||||||||
451 KENLFFVMEYLNGGDLMYHIQSCHKFDLSRATFYAAEIILGLQFLHSKGI 500
             .         .
```

Fig. 36 (Cont.)

```
501 VYRDLKLDNILLDKDGHIKIADFGMCKENMLGDAKTNTFCGTPDYIAPEI 550
    ||||||||||||||||||||||||||||||||||||||||||||||||||
501 VYRDLKLDNILLDKDGHIKIADFGMCKENMLGDAKTNTFCGTPDYIAPEI 550
              .         .         .         .
551 LLGQKYNHSVDWWSFGVLLYEMLIGQSPFHGQDEEELFHSIRMDNPFYPR 600
    ||||||||||||||||||||||||||||||||||||||||||||||||||
551 LLGQKYNHSVDWWSFGVLLYEMLIGQSPFHGQDEEELFHSIRMDNPFYPR 600
              .         .
601 WLEKEAKDLLVK..VRSEAKSVFIR 623
    ||||||||||||  ||   | . :|
601 WLEKEAKDLLVKLFVREPEKRLGVR 625
```

Fig. 36 (Cont.)